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IDIOSYNCRASIES

BY

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CONTENTS.

	PAGE
INTRODUCTION	7
PSYCHOLOGICAL IDIOSYNCRASIES	22
PHYSIOLOGICAL IDIOSYNCRASIES	28
Site of the Manifestations of Hypersensitiveness	58
FOOD IDIOSYNCRASIES	62
IDIOSYNCRASIES TO DRUGS	70
Cutaneous Manifestations of Hypersensitiveness	83
ASTHMA	91
HAY FEVER	103
OTHER ALLERGIC DISEASES	104
DISEASES POSSIBLY ALLERGIC OR DUE TO HYPERSENSITIVENESS	111
INDEX	116

INTRODUCTION.

Idiosyncrasy [ἰδιοσυγκράσια (ἴδιος = personal, and σύγκρασις = a mixing together) = a peculiar temperament or habit of body] has been frequently defined, but it would probably be unprofitable and certainly wearisome to recite and criticize them all. According to the Oxford Dictionary the word has three senses (1) a physical constitution peculiar to an individual, now only in medical use, (2) the mental constitution peculiar to a person or class of persons; a view or feeling, a liking or aversion, and (3) a mode of expression peculiar to an author. Thus Sir Edmund Gosse¹ recently spoke of "the complete idiosyncrasy of Samuel Johnson's prose" revealed in *Lobo*, his first publication in prose, as showing "the determined cultivation of discipline in the arrangement and construction of sentences, the love of antithesis, the indulgence to the ear in rhythm, and,

¹ Gosse, E., *Sunday Times*, 20 March, 1927.

IDIOSYNCRASIES

above all, the contrast cunningly introduced between solemnity and familiarity." But with this rather special use of the word, which would seem to be practically synonymous with style, it is hardly necessary to deal further.

Idiosyncrasies of course vary in their degree; there is a gradual transition from the average susceptibility in two directions, to the two extremes of insusceptibility and of hypersusceptibility, the latter supplying the most dramatic examples of idiosyncrasy; between these two poles there are many minor forms of idiosyncrasy.

The word idiosyncrasy (*ἰδιοσυγκράσια*) occurs in Liddell and Scott's dictionary with a reference to the *Tetrabiblos* (called the "Bible of Astrology") of Claudius Ptolemaeus (100-178 A.D.) an Egyptian mathematician, astronomer, and geographer; *ἰδιοσυγκρισία* was used by Sectus Empiricus (A.D. 225?), and *ἰδιοσύγκρισις* by Dioscorides (A.D. 100?). D'Arcy Power¹ translates as "idiosyncrasies" the Latin

¹ Power, D'Arcy. *Proc. Roy. Soc. Med.*, 1926, xx (Sect. Compar. Med.) 2.

IDIOSYNCRASIES

propria employed by Pliny in the following passage. "The Art of Medicine hardly admits any precepts of general application, and even cattle doctors since they cannot learn the idiosyncrasies of dumb animals insist on observation rather than on theories in cases of disease." In English the word appears in the seventeenth century: Francis Hering or Herring (obit 1628) wrote a small work of 37 pages in 1604 against wearing amulets containing arsenic as preservatives against the plague, and in it (page 29) occurs the following dictum: "The sympathys or antipathys of poisons together with the forces and secret insults of contagious seminaries, are unknown to the Physician. The idiosyncrasye, or particular Natures (as Galen called them) are unknowen, and (for ought we can see) incomprehensible unto humane imbecillitie." Sir Thomas Browne¹ wrote "Whether quails from any idiosyncrasy or peculiarity of constitution, do innocently feed upon hellebore, or rather sometimes but medically

¹ Browne, T. *Pseudodoxia Epidemica*, III, xxviii, edition 1672, p. 209.

IDIOSYNCRASIES

use the same ;” he described himself as “ of a constitution so general that it consorts and sympathiseth with all things. I have no antipathy, or rather idiosyncrasie, in dyet, humour, air, anything ” (*Religio Medici*, Part 2, Section 1). In 1690 J. P. Albrecht of Nuremberg wrote “ De singulari quorundam hominum idiosyncrasia.” The learned George Berkeley, Bishop of Cloyne, in *Siris, Philosophical Reflections concerning the Virtues of Tar Water* (1744), published in his sixtieth year, refers to “ Something in the idiosyncrasy of the patient that puzzles the physician.” These quotations show that the word had the same significance as it now has ; but even a hundred years ago its use seems to have been somewhat restricted, if we may judge from a review of six books on dietetics in the *Edinburgh Review* (1828, XLVII, 37) in which reference is made to “ the special and apparently capricious varieties of digestive power, which the learned call idiosyncrasy :” the reviewer goes on “ We see daily, among men of the same race and the same habits that one is poisoned

IDIOSYNCRASIES

by eggs, and another by honey, almonds, or cheese; another finds an antidote to dyspepsy in plum-pudding or mince-pie, and at the same time suffers from bread as from a poison."

Definition. Idiosyncrasy may be defined as an abnormal reaction in an otherwise normal person, which may be either on the one hand greatly exaggerated or on the other hand greatly diminished; more briefly it may be described as an unusual physiological personal equation.

It is thus distinguished from the abnormal effects seen in disease, for example on the one hand the more severe response to certain drugs (e.g. calomel and potassium iodide) in kidney disease when they cannot be properly eliminated, and on the other hand the tolerance to large doses in other diseases, such as of iodides in tertiary syphilis, opium in pain, and the reputed failure of digitalis to influence the heart in fever. Although idiosyncrasies have thus been distinguished from the modified and chiefly the exaggerated effects of drugs in disease, they

IDIOSYNCRASIES

may produce well marked and even severe symptoms. Abnormalities, such as colour blindness, and diseases such as haemophilia, it must be admitted, might not be thought to be excluded by the terms of this definition ; but nevertheless they do not come within the generally recognised four quarters of the word's meaning.

Idiosyncrasies, being functional aberrations, are in a different category from the effects of definite organic defects, such as short-sight, the day blindness of albinos due to lack of pigment, the night blindness of retinitis pigmentosa. But no doubt they depend on some modification of the physico-chemical structure of protoplasm, analogous to the arrangements of the electrons in the atom. More than forty years ago Jonathan Hutchinson argued that developmental defects, such as coloboma of the iris, hare-lip, clefts in the eyelid, and absence of the levator palpebrae muscle, are congenital idiosyncrasies of structure ; but this view though logically defensible is tantamount to using the

IDIOSYNCRASIES

word idiosyncrasy to describe a gross anatomical lesion instead of confining it to an abnormal physiological reaction, the structural basis of which may indeed be assumed, but is beyond our powers to recognise. Idiosyncrasy is a semi-popular rather than a scientific term in physiology, pathology, or psychology, and it may therefore be well to mention some other conditions which may have relation to it.

Allergy (ἄλλος = other, and ἐργία¹ = action) was introduced by von Pirquet in 1911 to describe all forms of altered reactivity of the organism, whether according to the time, early, accelerated, delayed, according to quantity, exaggerated, diminished or abolished, or according to quality, colour. It therefore includes both hypersensitiveness and immunity, but it is now so commonly regarded as synonymous with hypersensitiveness and

¹ There does not appear to be such a Greek word as ἐργία, though there is one connoting the opposite condition α-ἐργία = not working, idleness. But as ἐργία appears in von Pirquet's paper, this, rather than the more obvious ἔργον = work or ἐνέργεια = action, is quoted.

IDIOSYNCRASIES

anaphylaxis, which is not the original meaning attached to it, that a fresh name *anergy* is sometimes used to express extreme insensitiveness. As von Pirquet¹ employed it, allergy is the equivalent of idiosyncrasy, but now that allergy has come to be regarded as another name for anaphylaxis a distinction has been drawn between allergy and idiosyncrasy.

Anaphylaxis (*ἀνα* = a negative prefix and *φύλαξις* = protection), meaning the converse of immunity, was constructed by Charles Richet and Portier² in 1902 to describe the hypersensitiveness produced by one injection of a poisonous protein to a subsequent non-toxic dose. It was soon proved, as indeed Magendie (1839) and Flexner³ (1894) had previously noticed, that the responsible cause of the changed reactivity was the protein and not the poison, so the original significance of the word was lost. Anaphylaxis is

¹ Von Pirquet, C. E., *Arch. Int. Med.*, Chicago, 1911, VII, 259.

² Portier et Richet, *Compt. rend. Soc. biol.*, Paris, 1902, LIV, 170.

³ Flexner, S., *Med. News*, N.Y., 1894, LVX, 116.

IDIOSYNCRASIES

therefore an acquired hypersensitiveness to a foreign protein, and depends upon an antigen-antibody reaction ; it explains some, but not all, cases of idiosyncrasy.

To recapitulate, all cases of anaphylaxis come under the original meaning of allergy, namely altered reaction, but some only of the allergic manifestations are anaphylactic.

Diathesis (διάθεσις = disposition) is an old word much in vogue until the advent of bacteriology drove it out of favour as being by comparison with visible micro-organisms a vague old-world phantasy. The French, however, remained attached longer than other nations to the conception of diatheses, especially to the arthritic diathesis. But championship of the diathesis was not wholly absent elsewhere, for in 1908 Dyce Duckworth¹ proclaimed his belief in four diatheses, which recall the ancient temperaments : he pleaded for the recognition of the arthritic, the scrofulous or lymphatic, the nervous, and the bilious diatheses ; since that date increased

¹ Duckworth, D., *Lancet*, 1908, I, 800.

IDIOSYNCRASIES

knowledge of heredity and biochemical research have justified a modified and more scientific conception of diatheses, and the anthropometric investigation of the constitutional factors in the etiology of disease has brought the importance of diatheses to the fore. Diatheses, such as the exudative lymphatic, the spasmophilic, the neuro-arthritic, and the hypersthenic gastric which tends to cause peptic ulcer (Hurst¹) are now in evidence. Diathesis was defined as any bodily condition of prolonged peculiarity of health giving proclivity to definite forms of disease, or more briefly as "a persisting morbid proclivity" by Jonathan Hutchinson² who regarded idiosyncrasy as "indeed to a large extent nothing but diathesis brought to a point" and as "individuality run mad." There are, however, distinct differences between diatheses and idiosyncrasies; diatheses definitely tend to the development of

¹ Hurst, A. F., *Essays and Addresses on Digestive and Nervous Diseases*, etc., p. 19, 1924.

² Hutchinson, J., *The Pedigree of Disease, Six Lectures on Temperament, Idiosyncrasy and Diathesis*, London, 1884.

IDIOSYNCRASIES

disease, for example the scrofulous diathesis of our forebears favours the onset of tuberculosis; idiosyncrasies are abnormal reactions but do not necessarily dispose to disease. Diatheses are essentially hereditary and much more specifically so than idiosyncrasies, for in a diathesis there is a tendency to one morbid change, such as tuberculosis or peptic ulcer of the stomach or duodenum, whereas in idiosyncrasies the hereditary factor is usually a more widespread supersensitiveness or insensitiveness, the first of which tends later to crystallize out in some particular direction, it may be eczema, asthma, or sometimes to some particular food.

Constitution or the bodily make-up of the individual has been defined by Knud Faber¹ as "the nature of the body, including under this all inherent properties, such as the anatomical structure of the body, its morphological composition, as well as the functioning properties of the separate organs and cells." Con-

¹ Faber, Knud., *Nosography in Modern Internal Medicine*, p. 198, New York, 1923.

IDIOSYNCRASIES

stitution therefore includes hereditary variations from the average both in structure and function, and of the latter "the inborn errors of metabolism" or "chemical malformations" so happily named by Sir Archibald Garrod, are examples; they may be advantageous, harmless, though of scientific interest, or pathological, and therefore concern everyone, normal or otherwise. Although definitions are proverbially dangerous, clear thinking depends on an accurate use of terms, and it is therefore well to have a distinct notion of the relation of constitution to diathesis. Diathesis has been defined as a "persisting morbid proclivity" and so is a morbid constitution. Draper¹, who defined constitution as "the aggregate of hereditary characters influenced more or less by environment, which determines the individual's reaction, successful or unsuccessful to the stress of environment," has isolated a number of morbid forms of constitution which are practically the same as what others call diatheses. The constitutional varia-

¹ Draper, G., *Human Constitutions*, 1924.

IDIOSYNCRASIES

tions of function may be the basis of idiosyncrasies.

Temperament, now employed mainly in a psychological sense, was formerly much in medical use and was originally founded on a physiological basis, the four temperaments being established on the lines of the ancient humoral conceptions, namely the choleric or bilious, the phlegmatic, the melancholic, and the sanguine. Hutchinson in 1884 defined temperament as "the sum of the physical peculiarities of an individual, exclusive of all definite tendencies to disease," thus separating temperament from diathesis and making it of less importance from a medical point of view, and so but distantly related to, at any rate medical, idiosyncrasies. Alexander Stewart, who in 1887 produced a large book on "*Our Temperaments*" with many quotations, recognized four pure temperaments: the sanguine, bilious, lymphatic, and nervous, and regarded temperament as the association of certain mental with certain physical peculiarities. Psychologists on the other hand have regarded temperament as a

IDIOSYNCRASIES

type of mental character with tendencies to certain forms of emotion, Wundt defining them according to the strength of the emotions and the rate at which they alter ; thus in the choleric temperament the emotions are strong and change quickly, in the melancholic strong and slow, in the phlegmatic weak and slow, and in the sanguine weak and quick.

Idiosyncrasy is usually applied to exaggerated susceptibility, but logically, like allergy, it connotes also the opposite condition of abnormal insensibility, in which the individual is remarkable for his " phlegm " or thick-skinned nature, for his ostrich-like digestion, tolerance to drugs, and resistance to infections, and biting flies and insects. This hypo-sensitive group of idiosyncrasies is less easy to illustrate, because, for one reason, it is difficult to eliminate acquired immunity or tolerance, such as has been ascribed to the arsenic eaters of Styria.

Idiosyncrasies have been divided into (i) psychological or mental, and (ii) those more familiar and of greater medical interest concerned with the body and

IDIOSYNCRASIES

called, possibly for sake of contrast, physical; but "physical" is perhaps not a suitable adjective, for it might be interpreted as meaning structural and the outcome of gross change, such as a malformation visible to the naked eye; the descriptive title "physiological" would therefore be better than "physical."

PSYCHOLOGICAL IDIOSYNCRASIES.

(1) Psychological idiosyncrasies must be distinguished from eccentricities, whether of geniuses or others, for being concerned with abnormalities of manner and conduct, they may merge into mental disorder. Psychical tics of a harmless character might be thought to resemble idiosyncrasies, for example Dr. Samuel Johnson, whose strange gestures and grimaces may be regarded as evidence of habit spasm or a physical tic, was impelled to touch certain posts, to count his steps carefully as he walked along the streets, and even to retrace his steps to complete this duty. But tics are evidence of degeneracy and of a neuro-pathic taint, which may, like idiosyncrasies, be hereditary. In a tic there is an irresistible impulse to do something, whether it be trivial or of a serious nature. In the other direction idiosyncrasies help to make up character by forming distinctive

IDIOSYNCRASIES

traits, and so merge into temperamental features.

Psychological idiosyncrasies may, like the more familiar abnormal physiological reactions, be formally separated into the two groups of (1) abnormal insensitiveness to mental stimuli, e.g. the peculiarly thick-skinned individuals who are not morbidly selfish, proud, or the subjects of a disease, such as myxoedema, which blunts sensibility, (2) greatly exaggerated sensitiveness, which includes unusual antipathies and sympathies. Brief reference to these antipathies may now be made. It has been suggested that some apparently unreasonable antipathies may really be modified idiosyncrasies of physical origin, or alternatively may be due to some change in the sense organs.

According to Shylock (*Merchant of Venice*, Act IV, Scene 1)

“ Some men there are love not a gaping pig
Some that are mad if they behold a cat.”

A horror of cats affected such prominent men as Napoleon, Wellington, Lord Roberts, Henry III of France; Tycho Brahé fainted at the sight of a fox, Marshal

IDIOSYNCRASIES

d'Albert at that of a pig, and the Duc d'Epéron at a leveret but not at a hare. The smell of fish was most obnoxious to Roger Ascham¹ and was said to have made his contemporary Erasmus feel feverish; and the hereditary antipathy to the odour of cheese has been sufficiently strong to cause syncope. It might be possible to explain these effects as analogous to horse-, dog-, and cat-asthma and due to inhalation of animal protein. Dr. Mackenzie Wallis has told me of two patients with an antipathy to cats, in whom skin tests showed sensitiveness to cat extract and minute injections of that extract brought about de-sensitization, so that the antipathy disappeared. In other instances it would seem more probable that such strange antipathies depend on some peculiarity of the ideational and emotional centres, and so are really evidence of disordered intellect and imagination, and are due to auto-suggestion and hysteria. Thus a clergyman fainted whenever a

¹ Life of Erasmus by John Jortin, p. 581, 1758.

IDIOSYNCRASIES

certain verse in Jeremiah was read ; and another man swooned at the mention of a surgical operation ; a third became alarmingly giddy whenever a great height was described. What explanation shall be given of the "natural hydrophobiacs"¹ who as a hereditary peculiarity dislike fluids so much that even when feverish they refrain from drinking ?

Other cases may perhaps be explained by the influence of some memory buried in the unconscious mind. Robert Boyle² (1627-1691), to whom medicine owes much in many ways, especially for his advocacy of simple medicines instead of the elaborate mixtures then in vogue, fainted when he heard the sound of splashing water, an example which one Nicanor, according to Hippocrates, had set by doing likewise at the music of the flute. Some immediate personal dislikes, which are the converse of love at first sight, may have the same origin

¹ Hervé, G., *Bull. Soc. franç. d'hist. méd.*, Paris, 1924, xviii, 402.

² Millingen, J. G., *Curiosities of Medical Experience*, 1837, vol. II, p. 246.

IDIOSYNCRASIES

or be in some queer way instinctive. It has been suggested that incompatibility of married couples may possibly have some relation to incompatibility of their red blood corpuscles, but in the light of the four blood groups and a fair number of happy marriages, this seems rather a startling flight of fancy.¹

The unreasoning character of personal antipathies was well expressed in Martial's famous epigram (I. 32)—

“ Non amo te, Sabidi, nec possum dicere quare
“ Hoc tantum possum dicere, non amo te,”

Tom Brown (1663-1704), “ of facetious memory,” when an unruly undergraduate at Christ Church, Oxford, was “ hauled ” by the Dean, Dr. John Fell (1625-1686), who promised to overlook his misdeeds if he could translate the above epigram *ex tempore*, and thus unwittingly made his name known, in a way that it would not otherwise have been, until this present, for Brown promptly replied with the quatrain

“ I do not like you, Dr. Fell—
The reason why I cannot tell ;
But this I know, and know full well,
I do not like you, Dr. Fell.”

¹ Williams, L., *Empire Review*, 1925, XLII, 94.

IDIOSYNCRASIES

The importance of mental idiosyncrasies, such as antipathies expressed in shades of manner, in ordinary life need not be laboured ; in political emergencies they may have a momentous influence on the fate of nations.

PHYSIOLOGICAL IDIOSYNCRASIES.

Physiological idiosyncrasies, or abnormal reactions in otherwise average, that is normal, persons, are of practical importance in medicine. Their occurrence, though not very common, makes it difficult to elevate medicine to the status of an exact science like mathematics. Laboratory methods have done so much for the advance of medical science because the conditions can be so carefully controlled as to be made simple and cleanly cut as compared with those in the sick man. But just for this reason the subject of idiosyncrasies deserves consideration, for they help to explain why patients do not always react with the uniformity of laboratory animals.

Experiments made with the object of determining the action of a drug, cannot take into consideration the inborn or acquired susceptibilities known as idiosyncrasies which in the human subject

IDIOSYNCRASIES

occasionally upset all calculations. Their existence emphasises the importance of remembering that the treatment of each patient is a new problem, for she or he is a complicated organism reacting in their own way to a stimulus, and not a machine out of order as the result of occupation by some "morbid entity." There is much individual variation; for instance in regard to sensitiveness to pain, which is the warning given by disease; to take a common-place example, what a difference there is in the way that a dentist's attentions to the teeth affect different people. As pain is certainly the most frequent and perhaps the most important of all symptoms, a method of estimating a person's sensitiveness would obviously be of value. Libman¹ has practised a simple mechanical plan for years, namely pressure by the thumb upon the tip of the mastoid bone, behind the ear, which does not cause pain, and then against the styloid process, thus stimulating a branch of the great

¹ Libman, E., *Trans. Assoc. Am. Phys.. Phila.*, 1926, XLI, 305.

IDIOSYNCRASIES

auricular nerve, and exciting pain in some persons; possibly a more exact measurement might be obtained by employing an instrument which would record the pressure exerted, on the lines of Lipschutz's¹ "sensimeter" designed to gauge the degree of sensitiveness in cutaneous areas. Some persons do not feel any pain, and may be called hypo-sensitive, whereas others complain excessively and are hypersensitive; between these two extremes come what may be regarded as the average or normal persons as judged by their susceptibility to pain. The same classification may be adopted with regard to other reactions. Idiosyncrasies are due to altered susceptibility or sensitiveness, and of the two directions in which sensitiveness may be changed the most frequent and the most striking is that in which it is much increased. It will therefore be well to consider briefly the subject of hypersensitiveness.

Hypersensitiveness from a physiological point of view in animals can be pro-

¹ Lipschutz, E., *Am. Journ. Med. Sc.*, Phila., 1927, CLXXIII, 93.

IDIOSYNCRASIES

duced only by proteins which give rise to the formation of antibodies (antigens) which antagonize and tend to neutralize the "foreign" protein; human beings, however, can apparently be sensitized to other substances, such as drugs, and even to physical agents—light, heat, cold, injury. Hypersensitiveness has been divided into two kinds by Coca and Cooke¹ (A) Normal hypersensitiveness (i) seen in the so-called serum disease which so often follows injection of an anti-toxic serum, such as anti-diphtheritic and anti-streptococcic, and (ii) the skin reactions produced by contact with certain plants—dermatitis venenata, and (B) abnormal hypersensitiveness, (i) atopic hypersensitiveness, (ii) anaphylaxis, (iii) the hypersensitiveness of infections.

(A) *Normal hypersensitiveness*, if indeed the affix hyper- is justified for the state of response given by most people, is of course not an idiosyncrasy; a brief reference, however, may be made to

¹ Coca, A. F., and Cooke, R. A., *Journ. Immunol.*, Baltimore, 1923, VIII, 163; see also Coca, A. F., *Essentials of Immunology*, 1925.

IDIOSYNCRASIES

it, as the exceptions to the rule might be regarded as examples of undue insusceptibility and so of the less recognized division of idiosyncrasies.

(i) In *serum disease* eight to twelve and occasionally more days after a first injection of serum signs and symptoms of an “anaphylactoid” character are prone to appear—namely fever, rashes of an erythematous, urticarial, measly, scarlatiniform character, itching, oedema, arthralgia, enlarged glands. The systolic blood pressure is low, the white blood corpuscles are diminished in number (leucopenia), and there is a relative increase in the mononuclear cells of the blood. Serum disease, which cannot be produced in animals, occurs in a varying percentage of all human beings receiving serum parenterally, i.e., not through the alimentary canal, the variations in incidence probably depending on the character of the serum, as that of some horses is much more prone to be effective; the percentage incidence has in different estimates varied from 8 to 80 per cent. when the serum has been administered

IDIOSYNCRASIES

under the skin or into the spinal canal, and is about 90 per cent. when given intravenously (Coca). It is interesting to note that serum disease is said to be much less frequent in American Indians (46 per cent.) than in whites (90 per cent.). The symptoms are seldom more than troublesome. In the rare instances of sudden death after a first injection of serum, of which Lamson¹ in 1924 collected 32 examples, there was probably a sufficient cause, such as asthma with fully developed hypersensitiveness, or, in a few instances, as in Dr. R. Langerhans' infant in 1896 to whom he gave a prophylactic injection of anti-diphtheritic serum, the presence of status lymphaticus, in which death may follow any slight cause. Among the rarer manifestations are purpura, haemorrhagic nephritis, colic with melaena, thus presenting the features of Henoch's purpura which would appear to be, like angio-neurotic oedema, an anaphylactoid state; polyneuritis with muscular atrophy of which Pollet collected 25

¹ Lamson, R. W., *Journ. Am. Med. Assoc.*, Chicago, 1924, LXXXII, 1091.

IDIOSYNCRASIES

examples, 18 being after the use of anti-tetanic serum ; and orchid-epididymitis, of which Clement¹ collected 12 examples. With large injections arthritic effusions may result and microscopically show evidence of inflammation indistinguishable from those in acute rheumatism (Boots and Swift²). The appearance of a rash on two, three, or even four occasions after one injection of horse serum has been ascribed to sensitization to different proteins of the serum, euglobulin, pseudo-globulin, and serum albumin (Dale and Hartley³). Davidson⁴ recognizes three forms of cutaneous rashes, the urticarial, which has been thought to appear usually about the ninth day and is perhaps due to euglobulin, the morbilliform appearing about the twelfth day and due to pseudo-globulins, and the circinate

¹ Clement, R., *Med. Press and Circ.*, 1927, CLXXIV, 67.

² Boots and Swift, *Journ. Am. Med. Assoc.*, Chicago, 1923, LXXX, 12.

³ Dale, H. H., and Hartley, P., *Biochem. Journ.*, Cambridge, 1916, x, 409.

⁴ Davidson, W. T. G. *Glasgow Med. Journ.*, 1919, xci, 321 ; 1919, xcii, 20, 75, 129, 182.

IDIOSYNCRASIES

which appears about the fourteenth day.

A second injection after an interval may be followed by symptoms resembling those of the serum sickness, though usually more severe, which of course are manifestations of true anaphylaxis; in 1924 Lamson collected 8 cases of death following a second injection of serum in man, which contrasts with the frequency of such anaphylactic death in animals.

(ii) *Dermatitis venenata* or cutaneous sensitiveness to contact with certain plants, the active agent being supposed to be an oleo-resin which has not this effect on the lower animals, is specially seen in gardeners and others who handle bulbs of lilies, tulips, the *Primula obconica*, and American poison ivy (*Rhus toxicodendron*) which, though not indigenous, has been introduced into this country. These, which are largely trade or occupational eruptions, are erythematous and vesicular, and may be accompanied by fever and malaise and followed by peeling. According to Coca 60 per cent. of the population are susceptible, and so it

IDIOSYNCRASIES

is regarded as a normal hypersensitiveness ; the remaining 40 per cent. should therefore be regarded as abnormal and examples of an idiosyncrasy in the direction of hyposensitiveness. It has been found that hypodermic injection of small quantities of the alcoholic extract of poison ivy confers varying degrees of clinical immunity to its usual effects, although skin tests show that the individual is still sensitive to it (Spain and Cooke¹). Full-blooded American Indians, who, as has been mentioned, are said not to be as frequently affected as whites by serum disease, are about equally sensitive to poison ivy (Deibert, Menger, and Wigglesworth²). As examples of dermatitis venenata are rare under the age of three years the question of acquired sensitiveness might conceivably arise, in spite of Coca's authoritative teaching.

Another form of universal hypersensitiveness appears to be the epidemic

¹ Spain, W. C., and Cooke, R. A., *Journ. Immunol.*, Baltimore, 1927, XIII, 93.

² Deibert, O., Menger, E. F., and Wigglesworth A. M., *Journ. Immunol.*, Baltimore, 1923, VIII, 287.

IDIOSYNCRASIES

asthma and skin eruption in Florence described by Ancona¹ as the result of contact with grain infested with larvae of *Pediculoides ventricosus*.

Spider poisoning (arachnidism) and the irritating bites of insects and animals might seem to require consideration, though at first sight it would appear that the position is quite different, there being a definite poison present. But a poison acts only on those who are susceptible to it, and some persons are remarkably insensitive to bites of mosquitoes, fleas, and so forth. Some doubt has been expressed whether or not spiders, at any rate in England, are poisonous, but in other countries there is evidence that spiders' bites are toxic; Bogen² mentions 150 cases of poisonous spider bites in America, and among the effects describes a raised systolic blood pressure and a leucocytosis

¹ Ancona, G. *Sperimentale*, 1922, LXXVI, 270, quoted by E. F. Grove, *Journ. Immunol.*, Baltimore, 1926, XII, 263.

² Bogen, E., *Arch. Int. Med.*, Chicago, 1926, XXXVIII, 623.

IDIOSYNCRASIES

which are the reverse of what is seen in anaphylactic shock.

The supposed effects of the bite of the tarantula in causing the dancing mania in the 16th and 17th centuries add a flavour of mystery and romance to the bites of spiders, and the psychological and hysterical sequels of the bites—tarantism or tarantulism—have stimulated the imagination of novelists.

Tobacco is probably the most familiar example of a substance to which there is universal sensitiveness in the first instance. Everyone must be acquainted, either personally or by observation, with the collapse, deadly faintness, and gastrointestinal rebellion of the young smoker who a little later in his career may get a rapid irritable heart; it is interesting to contrast these symptoms of hypersensitiveness with those which may occur in later life, and are mainly of a painful character, like angina pectoris in the chest, colic in the abdomen, and in the lower limbs cramp or intermittent claudication. It seems probable that these are due to spasm which appears to be

IDIOSYNCRASIES

excited more easily in arteriosclerotic than in healthy arteries. Smoking may, however, be the cause of irregular heart's action (arrhythmia) at any time of life, and more especially after the age of fifty when extra-systoles (intermittent pulse) are common and more readily induced. The late Sir Clifford Allbutt,¹ who like so many persons of a gouty stock was the subject of many minor idiosyncrasies, namely to drugs, tea and coffee, described his own experiences as follows, "One case is known to us of a man, whose general health is excellent, who is by no means a neurotic subject, and whose heart stands work well in all other respects, in whom intermittence of the heart may occur for many days if he remain for an hour or two in a room with many smokers. He dare not sit in a close smoking room or in the smoking compartment of a railway carriage. The intermittence may not begin until the next day, or the next but one, but then comes on with the certainty of a laboratory

¹ Allbutt, C., *System of Medicine* (Allbutt and Rolleston), 1906, Vol. II., Part I., p. 983.

IDIOSYNCRASIES

experiment ; it gets worse during the next day or two, and then gradually passes off in a few more days. He never suffers from any cardiac disorder unless exposed to tobacco, but this proclivity has hung about him for many years. He has no dislike to the drug, nor does he feel any immediate discomfort from it." Tolerance to tobacco is usually obtained in a short time, though some never succeed. In animals, as in man, tolerance to nicotine can be induced by repeated doses, but in neither is it so well marked as to morphine. It may be partial, so that one kind of tobacco can be smoked with impunity whereas another cannot ; some persons have to be content with cigarettes, others cannot manage a pipe though they are happy with a cigar. Among cigars there is of course much difference in their character and effects ; a famous physician gets tobacco deafness from Havana but not from Manila cigars. This idiosyncrasy is much less recognized than the analogous tobacco amblyopia which is usually ascribed to smoking shag in considerable

IDIOSYNCRASIES

quantities, one ounce a day in Hutchinson's cases. The liability to tobacco amblyopia may well be favoured by some inherent or hereditary factor; for identical symptoms may occur in life-long abstainers from both tobacco and alcohol (Maitland Ramsay¹). the latter being usually considered to favour the occurrence of tobacco amblyopia. Hutchinson² recorded examples of its occurrence in several members of a family: the mother, who did not smoke, had the same, but permanent, impairment of vision that her sons acquired from smoking but recovered from when they abstained. Tolerance may be modified or even abolished by disease, for example influenza, and often gets less with advancing years; this may be due to several factors, to impaired resistance, to arteriosclerosis, and to diminished renal excretion (Maitland Ramsay).

(B) *Abnormal hypersensitiveness* or

¹ Maitland Ramsay, Reports of St. Andrews (James Mackenzie) Institute for Clinical Research, 1926, III, 23.

² Hutchinson, J., *The Pedigree of Disease*, p. 38, 1884.

IDIOSYNCRASIES

idiopathies, for the two terms are synonymous, have, as already mentioned, been divided by Coca and Cooke into (i) atopic, (ii) anaphylactic, and (iii) infective. These may also be summarized by saying that the first is inborn and determined by hereditary influence, whereas the other two are acquired, and reference will accordingly be made to them under the headings of (i) inborn, (ii) acquired. Hypersensitiveness to drugs is considered separately on page 70.

(i) Inborn hypersensitiveness has long been recognized and, though most probably as a Mendelian dominant character, appears in various forms, such as asthma, hay fever, urticaria, angio-neurotic oedema, gastro-intestinal disturbance, and, it has been suggested, pain in the urinary bladder, sick headache, and even some cases of epilepsy. In the same family different manifestations may be seen in brothers and sisters, and more than one form may occur in the same individual. When there is a bilateral heredity the incidence is higher than when it is unilateral only. According to Coca 7 per

IDIOSYNCRASIES

cent. of the white population in America have some form of inborn hypersensitiveness, 3.5 per cent. being in the form of hay fever or asthma. The adjective atopic (*ἀτοπία* = strangeness, extraordinary nature) has been applied by Coca and Cooke to hypersensitiveness in man due to hereditary or familial influence and characterized by the constant presence in the blood of specifically reacting substances, discovered by Praunitz and Kustner, called "atopic reagins" which are primarily responsible for the manifestations of hypersensitiveness. Thus when the blood of an atopic person is injected into the skin of a normal person, that area, but not the rest, of the body becomes sensitive to the atopens or substances, such as foods or pollens, which give a positive reaction in the atopic donor. In this way the atopic nature of a case of hypersensitiveness can be decided.

The relation of status lymphaticus to asthma, the association of which has been noted by Alexander and Paddock¹

¹ Alexander and Paddock, *Arch. Int. Med.*, Chicago, 1921, xxvii, 184.

IDIOSYNCRASIES

is of interest. Lymphatism is commonly regarded as an inborn defect, but Cameron,¹ who prefers to call it the status catarrhalis, regards it as the result of catarrhal infection of the mucous membranes dependent upon chronic nutritional defects partly inherited, partly environmental and dietetic. Symmers² ascribes the sudden death in status lymphaticus to anaphylaxis due to sensitization by repeated liberation of nucleo-protein from necroses in the germinal centres of the lymphatic glands, and it would therefore be conceivable that slighter degrees of this auto-sensitization might cause asthma.

(ii) *Acquired hypersensitiveness*: under this heading a few lines will be devoted to (a) anaphylaxis artificially produced by the therapeutic injection of antitoxic serums, such as antidiphtheritic and antistreptococcic, a subject on which an enormous amount of experimental work has been done on animals, and to

¹ Cameron, H. C., *Diseases of Children*, p. 95, 1926.

² Symmers, D., *Am. Journ. Med. Sc.*, Phila., 1918, CLVI, 40.

IDIOSYNCRASIES

(b) hypersensitiveness, the result of infection.

(a) Anaphylaxis: in man hypersensitiveness produced by an intravenous injection of a foreign protein, such as horse serum which is the usual medium for antitoxins, to a subsequent injection of the same protein in however small a quantity is well recognized, but is not seen with the same regularity as in laboratory animals. Indeed the manifestations of the anaphylactic reaction or shock produced by a second injection of the same protein are not the same in different species of animals; in guinea-pigs there is spasmodic contraction of the small bronchial tubes, thus reproducing the condition in human asthma, and, as guinea-pigs are specially sensitive, death often results; in rabbits the symptoms are chiefly circulatory, and in dogs abdominal, namely great vascular engorgement of the intestines and of the liver which shows focal necroses. In man anaphylactic shock is rare, as is shown by its exceptional occurrence in the large number of men who received

IDIOSYNCRASIES

anti-tetanic and anti-dysenteric serums during the War; but it undoubtedly occurs, and I have seen it in several patients with cerebrospinal fever, who, after receiving a number of injections of anti-meningococcic serum at a few days' interval then had another after a longer interval. It is therefore advisable to test persons who have previously had an injection of serum to see if they are still hypersensitive before giving an injection, so that, if they are, they can be de-sensitized by minute doses after the method of Besredka. Persons with in-born (atopic) hypersensitiveness, such as asthma excited by exposure to horse dandruff, may for this reason be in the same condition of anaphylaxis to horse serum as a previously normal person who has been artificially rendered anaphylactic by an injection of antitoxic serum. Why the liability to anaphylactic shock in man varies so much it is difficult to explain; it has been suggested that the condition of over-excitability of the vagus and parasympathetic, or more shortly vagotonia, may be the responsible factor.

IDIOSYNCRASIES

How far in man anaphylaxis may be caused by absorption through the inflamed, ulcerated, and otherwise altered mucous membrane of the alimentary canal of foreign proteins which have not undergone the usual changes in digestion is rather uncertain (vide p. 64). But the absorption of proteins, both vegetable and bacterial, from the respiratory tract appears to be established. The word anaphylaxis has been widely and, it must be admitted, often loosely used to explain a number of diseases; for from the immunological point of view it is confined to those cases only in which antibodies are produced in response to the presence of an antigen which is generally believed to be always protein in nature.

(b) Hypersensitiveness due to infection of various kinds, especially of the respiratory tract giving rise to "bacterial" asthma in the later years of life, but also of the teeth, tonsils, nasal mucosa, intestine, gall bladder, and appendix are recognized as causes of various anaphylactoid phenomena. The cases of bacterial hypersensitiveness seldom give

IDIOSYNCRASIES

positive results with cutaneous tests; Schiff¹ indeed, getting a positive result in about 1 per cent. only by the scratch method which is not sensitive enough, has abandoned its use; the intradermic method on the other hand gives many pseudo reactions which makes their interpretation difficult. Calmette's ophthalmic reaction and von Pirquet's and Moro's cutaneous reactions are based on sensitization to tuberculous infection, and a number of other micro-organisms, such as *Bacillus mallei*, *B. typhosus*, and *Treponema pallidum*, give rise to hypersensitiveness which can be tested for by similar reactions. The close relations of hypersensitiveness and immunity, which are not, as Richet when inventing the name "anaphylaxis" originally thought, at the opposite poles, have been further shown by investigations in connection with tuberculosis carried out by Krause and Willis², who thus support the well-established view that the

¹ Schiff, N. S., *Internat. Clinics*, Phila., 1926, 36 ser., Vol. III, p. 151.

² Krause, A. K., and Willis, H. S., *Am. Rev. Tuberc.*, 1926, XIV, 316.

IDIOSYNCRASIES

tissue effects of allergy constitute a phase in the development of immunity.

Special idiosyncrasy for infectious diseases: some persons appear to be prone to contract any disease that is prevalent or to suffer repeatedly from the same disease, for example, pneumonia, erysipelas, and influenza. This question is not without difficulties, for in some cases of recurrent scarlet fever, measles, and typhoid doubt may arise as to the correct diagnosis of the several attacks from recurrent desquamative scarlatini-form erythema, German measles (rubella or röteln), the fourth disease, and paratyphoid fever. Some persons lack the power of forming antibodies and developing immunity, and this would constitute idiosyncrasy. As Zinsser¹ suggests, the special liability to catch diseases and to have the same disease more than once may be due to hypersensitiveness to bacterial proteins.

¹ Zinsser, H., *Infection and Resistance*, p. 435, 1918.

IDIOSYNCRASIES

MANIFESTATIONS OF SENSITIVENESS EXCITED BY PHYSICAL FACTORS.

In a number of cases clinical manifestations of an "anaphylactoid" character are excited by purely physical factors, such as sun and other kinds of light, x-rays, heat, cold, and mechanical irritation. Duke¹, who has specially studied this subject, reminds us that asthmatic patients are influenced by these factors, which may therefore be considered as at least contributory, and that in many cases of asthma, hay-fever, urticaria, eczema and so forth exposure to the antigen cannot be established. Duke's examination of such cases showed that only one physical agent, most frequently heat, brought out the symptoms, and the hypothesis was put forward that persons with hypersensitive tendencies may be sensitive to a protein body which is liberated from the cutaneous cells by the action of some one physical factor only, whether it be heat, cold, sunlight,

¹ Duke, W. W., *Journ. Am. Med. Assoc.*, Chicago, 1924, LXXXIII, 3 ; 1925, LXXXIV, 736.

IDIOSYNCRASIES

or mechanical trauma. The reaction which follows may be either local to the area affected or general, and then may be shown by collapse. Lewis and Grant's¹ observations that mechanical and other forms of irritation normally liberate a histamine-like body (referred to as H-Substance) from the cells of the skin with the resulting production of urticaria support Duke's hypothesis. Lewis and his co-workers² found that various physical factors, including ultra-violet rays, leave the cutaneous blood-vessels in a peculiar condition characterized by permanent dilatation, increased permeability leading to oedema, whealing and blistering, by loss of contractile power and of reaction to adrenalin, pituitrin, and histamine. Lewis (1927) concludes that the skin reactions produced by physical reactions precisely resemble the anaphylactic skin

¹ Lewis, T., and Grant, R. T., *Heart*, London, 1924, XI, 209.

² Lewis, T., *Heart*, London, 1926, XIII, 153; and *The Blood Vessels of the Human Skin and their Responses*, 1927.

² Lewis, T., and Zotterman, Y., *Heart*, London, 1926, XII, 203.

IDIOSYNCRASIES

reaction and that produced by histamine, and further that a fundamental factor in the anaphylactic reaction is the liberation of the histamine-like substance. These observations explain the urticaria due to light, heat, or cold, and possibly the bad effect on patients with tuberculosis (who are thereby sensitized) of undue exposure to the sun.

A rare but interesting example of cutaneous hypersensitiveness to the direct rays of the sun is shewn by the production in spring and summer of blisters and scarring, named by Bazin in 1862 *hydroa vacciniforme vel aestivale*, and also by the less sharply cut and less severe group of summer prurigo described by Jonathan Hutchinson¹ in 1879. In 1898 McCall Anderson² reported cases of *hydroa vacciniforme* in association with haematoporphyrinuria, and since then A. E. Garrod³ has brought forward evidence to show

¹ Hutchinson, J., *Lectures on Rare Diseases of the Skin*, p. 126, 1879.

² McCall Anderson, *Brit. Journ. Dermat.*, 1898, x, 1.

³ Garrod, A. E., *Inborn Errors of Metabolism*, Second Edition, 1923.

IDIOSYNCRASIES

that congenital porphyrinuria is an inborn error of metabolism or a "chemical malformation", which may be associated with pink teeth and pigmentation of the bony skeleton (Mackey and Garrod¹; Ashby²; Sato and Takahashi³), and by sensitizing the skin to sunlight be responsible for hydroa vacciniforme. According to this view the skin sensitiveness is secondary to the congenital metabolic defect. It appears, however, that the cases of hydroa vacciniforme, which are prone to occur in families, fall into two groups, those with and those without porphyrinuria, and that congenital porphyrinuria may occur without sensitivity to light; Gray⁴ has therefore criticized the explanation that the porphyrinuria is the primary factor and, like Duke, argues that the skin is primarily sensitive

¹ Mackey, L., and Garrod, A. E., *Quart. Journ. Med.*, Oxford, 1921-2, xv, 319; 1925-6, xix, 357.

² Ashby, H. T., *ibid.*, 1925-6, xix, 375.

³ Sato, A., and Takahashi, H., *Am. Journ. Dis. Child.*, 1926, xxxiii, 325.

⁴ Gray, A. M. H., *Quart. Journ. Med.*, Oxford, 1925-26, xix, 381.

IDIOSYNCRASIES

to light, and that the porphyrin can also be produced by the action of light on immature red cells. Experimental injection of haematoporphyrin certainly shows that it is, like eosin, a photo-sensitizing agent, but the resulting skin lesion is not exactly the same as in hydroa vacciniforme. The question of the relation between hydroa vacciniforme and porphyrinuria is interesting, but whatever view be eventually taken there is no doubt that the skin is unduly sensitive to light, and that this peculiarity or idiosyncrasy is like others prone to run in families.

Skin sensitiveness to light varies in normal individuals, blonds being more sensitive and less able than brunettes to develop the defensive mechanism of pigmentation. Barber, Howitt, and Knott¹ divide light sensitiveness into two groups (i) the juvenile, including the rare cases of congenital porphyrinuria and the less severe condition of hydroa vacciniforme in early childhood described

¹ Barber, H. W., Howitt, F. D., and Knott, F. A., *Guy's Hosp. Reps.*, 1926, LXXVI, 314.

IDIOSYNCRASIES

by Bazin, in which they found porphyrin in the urine in two cases and porphyrin in the faeces in three, and (ii) the adult, including Hutchinson's summer prurigo and solar dermatitis, due to intestinal infection and the sensitizing action on the epidermal cells of a substance thus produced, either a decomposition product of protein, or more probably a bacterial protein. These patients show evidence of intestinal stasis and almost constantly of well marked hypochlorhydria.

X-rays and radium emanations damage the skin and tissues, and unfortunately there are numerous examples of permanent and serious injury, particularly squamous-celled carcinoma of the exposed skin, necessitating amputation of the hands and arms, sustained by radiologists, especially in the early days when these effects were not realized; writing in 1922 Ledoux-Lebard¹ estimated that a hundred radiologists had lost their lives as the result of their profession. More

¹ Ledoux-Lebard, R., *Paris méd.*, 1922, XII, 299.

IDIOSYNCRASIES

recently about twelve radiologists have succumbed to grave anaemia, and it may be noted that radium seems more prone than x-rays to cause this aplastic form of anaemia. Some of the early pioneers who did not take any precautions escaped these untoward effects, and the question of personal idiosyncrasy to the action of radiations thus raised has given rise to much discussion; it was philosophically considered by Colwell and Russ¹ who quote the answers to Arcelin's *questionnaire*: seven radiologists of repute believed that real idiosyncrasy existed and six took the opposite view. It would appear that there is a universal liability to react to x-rays, but that individuals undoubtedly show considerable variations in their response to the same doses; the experience of Dr. A. E. Barclay with x-rays and of Mr. Hayward Pinch of the Radium Institute, which they have kindly put at my disposal, would lead to the con-

¹ Colwell, H. A., and Russ, S., *Radium, X-rays, and the Living Cell*, p. 321, London, 1924.

IDIOSYNCRASIES

clusion that undoubted idiosyncrasy in the direction of extreme hypersensitiveness is rare, and that the real explanation of many reputed examples is undue exposure. The same individual may react differently at different times to the same dose ; there may be many factors responsible for this, and Mottram¹ has pointed out that a good blood supply to the part exposed increases the reaction, presumably on account of the secondary radiation from the iron of the haemoglobin (Knox).

Acquired hypersensitiveness to radiations has been described both in patients and radiologists, but is fortunately very rare, at any rate in a severe form. It is well recognized in the skin, and T. Lewis² has shewn that damage of the blood vessels by x-rays leaves them in a curious state of inability to respond to vaso-constrictor stimuli ; this may help to account for the acquired sensitiveness of skin areas after damage by x-rays.

¹ Mottram, J. C., *Brit. Journ. Radiol.* (B.I.R. Sect.), 1924, xxix, 174.

² Lewis, T., *Heart*, London, 1926, xiii, 153.

IDIOSYNCRASIES

SITE OF THE MANIFESTATIONS OF HYPERSENSITIVENESS

An individual who is hypersensitive may have manifestations in various parts of the body, in the skin as rashes, in the bronchi or mucous membrane of the nose as asthma or hay fever, in the alimentary canal as dyspepsia, diarrhoea, mucous colic, or enterospasm, in rare instances in the joints by swelling, and, it has been stated, in the brain as epilepsy or migraine (vide pp. 105, 110). Occasionally, as has been mentioned, two or more of these sites may be involved at the same time. What manifestation a given individual will present must depend on (i) local conditions, such as sensitization or altered power of reaction locally, as is suggested by the frequency with which bacterial bronchitis is followed by asthma, or on (ii) an irritable state of the commanding nervous centres for the respiratory or alimentary tracts.

The manifestations of idiosyncrasies are obvious on the skin in the form of rashes and oedema, and very probably

IDIOSYNCRASIES

are due to the advent by the blood stream of bodies which act on the cells of the skin in such a manner that a histamine-like body (Lewis and Grant¹) is liberated and affects the blood-vessels and also from the occurrence of pruritus or itching, the nerves. The mucous and muscular walls of the alimentary tract also frequently react, as is shewn by nausea, vomiting, diarrhoea, and colic. The condition called mucomembranous colitis, or probably more correctly mucous colic, as there is not necessarily any inflammation, is a combination of spasm and excessive secretion of mucus, which being retained in the bowel coagulates and forms skins or casts. There is thus a close resemblance to spasmodic asthma, an attack of which may terminate by the expulsion of a pellet of mucus and is followed by signs of bronchitis. Mucous colic and enterospasm therefore appear to be so closely allied to asthma as to merit the term

¹ Lewis, T., and Grant, R. T., *Heart*, London, 1926, xi, 209; Grant, R. T., *Brit. Journ. Dermat. and Syphil.*, London, 1926, xxxviii, 426.

IDIOSYNCRASIES

abdominal asthma. These spasmodic abdominal manifestations may come on after eating a protein-containing food to which the individual is unduly sensitive, and in some cases the local action may be analogous to the erythema produced in certain persons by a belladonna plaster, or to the paroxysm of hay fever caused by contact with pollens. But in instances in which the reaction is more widespread absorption takes place ; urticaria has long been recognized as associated with gastro-intestinal disturbance and has generally been regarded as secondary to it. But it is reasonable to consider that they may both be results of the same underlying cause—hypersensitiveness to some protein which of course is generally taken by the mouth ; it is indeed possible that a change similar to urticaria may occur in the stomach and intestines (internal urticaria), for haematemesis and urticaria have been known, though very rarely, to coincide ; further, angio-neurotic oedema, which is only an exaggerated form of urticaria, attacks mucous membranes, and Henoch's

IDIOSYNCRASIES

purpura, or cutaneous haemorrhages with abdominal pain imitating appendicitis or intussusception, is another analogous case. The urinary and the gall bladder may also be excited to spasm and so cause pain, thus imitating a gross organic lesion, such as calculus or cholecystitis. The nasal and bronchial walls are prone to suffer from the inhalation of pollens in hay fever, and of animal emanations (horse, cat, dog), house dust, many forms of powder and vegetable odours in asthma; in addition excitants from the alimentary canal, and the products of bacterial infection, especially of the bronchi themselves, induce asthma. The oedema and swelling of the bronchial tubes are analogous to the changes in urticaria, and Angel Money's description of asthma as nettlerash of the bronchi, which in the 'eighties seemed fanciful, may be justified. Asthma is occasionally associated with, or takes the place of, other manifestations of hypersensitiveness, such as urticaria or eczema.

FOOD IDIOSYNCRASIES.

As the alimentary canal is the part of the body *par excellence* for absorption of extrinsic material and as opportunities for its infection are both more numerous and on the whole more difficult to avoid than in the case of the respiratory tract, its importance as an inlet for sensitizing bodies which call forth idiosyncrasies is obvious. Foods introduce not only proteins, which, if absorbed without digestive modification, as the result of some insufficiency of the intestinal mucosa, may sensitize the organism, but also of course bacteria the products of which may likewise sensitize the body as a whole or set up acute inflammation (food poisoning) or both. Food idiosyncrasies have naturally long been known, as was expressed by Shakespeare "What's one man's poison, Signor, is another's meat or drink," and have created an enormous literature. It is possible that in the past some historical cases of

IDIOSYNCRASIES

poisoning were due to this cause. The number of different foods that have been incriminated is legion, as may be judged by the long list of food extracts which have been prepared to test the skin reactions in asthma and other idiopathies ; Duke¹ incidentally mentions a medical man who had undergone three hundred different skin tests with a negative result.

Food idiosyncrasies are commonest in early life and tend to disappear gradually in a few months, presumably as the result of unconscious de-sensitization, namely by eating very small quantities of the sensitizing food ; there is therefore something to be said for the stern parent or nurse who is not too lenient to " faddiness " on the part of the young. Food sensitization is seldom acquired ; but it may develop somewhat suddenly for some food, such as eggs, which has been taken previously without any untoward symptoms ; in some instances this is noticed after an interval of abstinence.

¹ Duke, W. E., *Journ. Am. Med. Assoc.*, Chicago, 1924, LXXXIII, 3.

IDIOSYNCRASIES

It is perhaps rather strange that patients with gastro-intestinal ulceration do not become sensitized to food proteins. Years ago horse serum was often given by the mouth for its healing influence on gastric ulcers, but I never saw serum sickness or hypersensitiveness. It is, however, stated that from inborn defect in the alimentary mucous membranes foreign proteins can pass unaltered into the blood of infants, and Storm van Leeuwen regards previous peptic ulcer and enteric fever as factors of some importance. Often there is a warning in the form of an antipathy to the offending food, but this is by no means constant, for the reverse, namely a keen relish, is not very rare. After the age of fifty a very distinguished physician became extremely sensitive to oysters, of which he was fond, without any previous evidence of gastro-intestinal disorder. The sensitiveness may be specific, for example for eggs of one species of bird or the milk of one mammal only. Sometimes it is only stale articles of diet, such as fish, which are harmful, and here the

IDIOSYNCRASIES

possibility of bacterial infection and the formation of toxic bodies must be taken into account.

Reference can be made to a few only of the numerous articles of diet which at one time or another have been concerned in bringing out idiosyncrasies. White of egg is one of the commonest recognized, but sometimes its evil influence, particularly in causing vomiting and diarrhoea, may be unsuspected, for example when occultly present, as in the glazing of buns. A man before a royal entertainment at dinner by his admirers begged that eggs should be omitted from the menu: although this was of course borne in mind, he suffered grievously because the soup had been cleared with white of egg. Eggs may also be unsuspected in cakes until vomiting reveals their presence. These symptoms of mysterious origin may be explained only when by some accident eggs are removed from the dietary. A medical friend consulted me for morning depression, a conviction that he was a bankrupt, and for pain over the gall bladder which

IDIOSYNCRASIES

was tender ; all these symptoms vanished when from force of circumstances he ceased to take the usual breakfast egg. An unusual manifestation of allergy to eggs is temporary impairment of vision (Hutchinson). Mistakes may occur in other ways—a man supposed to be sensitive to salmon was eventually proved to be affected only by the parsley scattered over the fish. Cow's milk in rare instances excites gastro-intestinal rebellion, particularly in infants, in whom symptoms come on from a quarter of an hour to five hours after it is taken. It may be responsible for eczema, urticaria, and asthma, or for more than one unpleasant penalty ; thus an unlucky infant of 10½ months had a widespread reaction in the form of mucous colic, vasomotor rhinitis, and angio-neurotic oedema (Walters¹). That some newly born infants cannot digest their mother's milk and suffer from vomiting, colic, and diarrhoea after each feed is well known ; it has usually been ascribed to a toxic factor in the mother or to the milk being " too

¹ Walters, A. M., *Lancet*, 1925, II, 220.

IDIOSYNCRASIES

rich." Lately it has been explained as due to hypersensitiveness which has been removed by injection of 1 to 5 c.c. of the mother's milk under the skin of the infant's abdomen (Sztark¹). Among early observations really dealing with the effects of hypersensitiveness an interesting one is the hereditary purgative effect of veal (Albrecht² (1690)). Honey has been accused of causing headache since the days of Xenophon, and of course its character varies considerably according to the flowers visited by the bees. Figs may set up pruritus, rice and many other articles of ordinary diet asthma. Strawberries may bring out a rash, and their influence on gouty people, who are so liable to idiosyncrasies especially in the direction of bringing out joints pains, is noteworthy; the eruption produced in a susceptible person by gooseberries has been known to reveal this constituent in soi-disant cham-

¹ Sztark, C. H., *Arch. de méd. des enf.*, Paris, 1921, xxiv, 555.

² Albrecht, J. P., Quoted by Hervé, G., *Bull. Soc. franç. d'hist. méd.*, Paris, 1924, xviii, 402.

IDIOSYNCRASIES

pagne. The manifestations due to various cereals are multiple ; oatmeal, cabbage, and carrots may cause itching and "eczema" ; beans and carrots nausea and vomiting. Migraine has been ascribed to eating chocolate (Pagniez¹) and beans (Lubbers²). Unless such sensitiveness is suspected, the results may be regarded as periodical attacks of "liver," biliousness, explosive toxaemias of intestinal origin, or auto-intoxication which recalls the blessed word "Mesopotamia."

Now that so many cases of indigestion have rightly been traced to a chronically inflamed gall bladder or appendix it is well to remember that all dyspepsias are not surgical, and that some are due to hypersensitiveness. From analysis of 300 consecutive patients with symptoms of hypersensitiveness Lentz³ found that operations had been more frequently performed upon them than on any other

¹ Pagniez. *Presse méd.*, Paris, 1921, xxix, 48.

² Lubbers, H. A., *Nederl. Tijdschr. v. Geneesk.*, Amsterdam, 1921, II, 1073.

³ Lentz, *New York Journ. Med.*, 1925, xxv, 368.

IDIOSYNCRASIES

groups of patients ; some indeed had been operated upon as many as thirteen times without benefit. Just as in Henoch's purpura (purpura with abdominal symptoms), so in asthmatics with abdominal pain the question of operation on the assumption that the pain is due to appendicitis rather than to a food idiopathy should always be carefully considered.

IDIOSYNCRASY TO DRUGS.

Idiosyncrasy to drugs as a matter of practical importance is now receiving a fair share of recognition, partly no doubt from the experience that to neglect a patient's protest of such and such a drug's unpleasant effect and to prescribe it all the same may come back like a boomerang on the practitioner and give him cause to remember the audacious experiment. Though stated not to be common, such idiosyncrasies are by no means rare, at least in their less dramatic forms; when presented with an anomalous rash one of the first things is to consider the possibility that it is due to medical treatment; for the erythematous rash produced by belladonna or quinine, or by a purgative enema, may suggest scarlet fever, and what is really the acne caused by iodides has been diagnosed as small-pox and the patient sent to a small-pox hospital to be returned to the certifier's discomfiture. Hydroa was

IDIOSYNCRASIES

described by Bazin of Paris in 1862 as a new disease, which Jonathan Hutchinson¹ considered was nearly always the result of iodides, a view far too exclusive in the light of present knowledge.

Idiosyncrasies to drugs should be divided, as Storm van Leeuwen² points out, into two groups (i) when the known toxic effects of large doses appear as the result of small doses ; thus in some individuals small amounts of alcohol produce drunkenness, minute doses of calomel salivation and excessive purgation, or a quarter of a grain of quinine an erythema on the legs, such as the late Dr. B. Yeo suffered from³ ; (ii) when the drug produces effects not seen in tolerant persons, for example morphine and bromides may cause mental excitement, the opposite of their usual action ; these are qualitative idiosyncrasies.

Though not containing foreign protein,

¹ Hutchinson, J., *Pedigree of Disease*, p. 5, 1884.

² Storm van Leeuwen, W., *Journ. Pharmacol. and Exper. Therap.*, 1924, xxiv, 25.

³ Yeo, B., *Trans. Clin. Soc. London*, 1889, xxii, 193.

IDIOSYNCRASIES

the manifestations produced by drugs have considerable resemblance to the anaphylactoid cutaneous reactions sometimes caused by foods and bacterial products, though asthma is rather rarely thus induced. In order to bring drug idiosyncrasies into line with those of foods it has been suggested that before exerting their action drugs enter into some physical or physico-chemical relation with the tissues of the body, and thus may so modify the proteins as to render them "foreign" and capable of sensitizing the individual. This is supported by the observations that similar eruptions may be produced by drugs of entirely different composition, a point insisted on by Storm van Leeuwen when speaking of qualitative idiosyncrasies; that one attack of a drug eruption increases the liability to others, so that a much smaller quantity is sufficient to produce it; and that the same drug may be followed by different effects in different individuals. It is significant that porphyrinuria, which can be produced in some patients by the long-continued

IDIOSYNCRASIES

administration of a few drugs, most frequently sulphonal and less often trional and tetronal, also occurs in rare instances as an inborn error of metabolism, and that the presence of porphyrin in the blood has been thought to sensitize the skin so that sunlight induces a peculiar skin eruption *hydra vaccini-forme vel aestivale* (Mackey and Garrod¹). It may also be mentioned that *ochronosis*, or inky ochre-like pigmentation of the cartilages, of which about 54 examples in all have been published, occurs in some cases of *alkaptonuria*, another inborn error of metabolism, and has also been observed after the repeated external application of carbolic acid.

The use of the term *anaphylaxis* is confined to the reactions occurring in connection with proteins which are the only substances known to act as antigens (or stimulants to the formation of antibodies); it is, however, possible that toxic glucosides may have this

¹ Mackey, L., and Garrod, A. E., *Quart. Journ. Med.*, Oxford, 1921-22, xv, 319.

IDIOSYNCRASIES

power (Ford¹), and as Pryde² points out, bacterial toxins, which are undoubtedly antigens, have not been proved to be protein in nature. Further, house dust, which may excite asthma, and pollen, which is responsible for hay-fever, have been found by Grove and Coca³ still to exert this effect when their extracts have been deprived of all trace of protein. It has been suggested to me by Professor W. E. Dixon that if sensitiveness is induced by a chemical substance, combined with a protein, the symptoms of hypersensitiveness might possibly be subsequently produced by the injection of the non-protein chemical substance alone. On the other hand Storm van Leeuwen⁴ argues that in normal persons drugs are always combined with other substances in the blood, whereas, from failure of the combining power of their blood,

¹ Ford, W. W., *Journ. Infect. Dis.*, Chicago, 1906, III, 191 ; 1907, IV, 434, 541.

² Pryde, J., *Recent Advances in Biochemistry*, p. 298, London, 1926.

³ Grove, E., and Coca, A. F., *Journ. Immunol.*, 1925, x, 471.

⁴ Storm van Leeuwen, W., *Journ. Pharmacol. and Exper. Therap.*, 1924, xxiv, 25.

IDIOSYNCRASIES

they are "free" in the blood of persons who are hypersensitive to those drugs, and that the drugs merely augment the action of sensitizing bodies which are present in the blood but otherwise would not be capable of causing symptoms of idiosyncrasy; this fits in with his view that the symptoms of qualitative idiosyncrasies are as a rule similar *inter se*.

The idea that drugs produce their unusual anaphylactoid reactions as the result of their modifications of the body proteins so that they act as "foreign" proteins is vigorously opposed by Coca, who not only protests that there is an entire lack of experimental basis for this view, but endorses Doerr's objection that it necessitates a practically instantaneous alteration of the body proteins in order to explain the very rapid occurrence of some fatal drug idiosyncrasies. The production of antibodies to drugs has not been satisfactorily established, and accordingly the use of the words anaphylaxis and anaphylactoid should be avoided in reference to drug idiosyncrasies which may be designated as allergic,

IDIOSYNCRASIES

meaning thereby an altered or abnormal reaction. As Coca points out, the specificity of drug idiosyncrasy is sharply limited and may be determined by the presence of a single chemical group, such as the methyl CH_3 .

The drugs which give rise to idiosyncrasies are those with a well-established reputation for exerting definitely beneficial effects, and include quinine and arsenic, which, it may be noted, are protoplasmic poisons, belladonna, opium, iodides and bromides, antipyretics of the coal tar series, salicylates, aspirin, and cocaine.

Extreme tolerance to drugs, which in some sensitive individuals may produce idiosyncrasies, are also known, especially in the case of the halogen compounds; epileptic patients often take large doses of bromides for long periods with impunity, and in cerebrospinal syphilis enormous doses of iodides are commonly well borne. Hutchinson (1884) mentioned a patient who took an ounce and a half of iodide daily for a week without any discomfort other than "a feeling of lassitude and

IDIOSYNCRASIES

want of tone." It has been suggested by Zinsser¹ that tolerance to drugs is due to cellular rather than to serum antagonism and therefore does not depend on the production of antibodies, as some have stated.

The exaggerated effects produced when, from kidney disease, their excretion from the body is diminished, so that accumulation results, must be discounted and not regarded as at any rate ordinary hypersensitiveness or idiosyncrasies, for in patients with nephritis mercury and calomel may easily cause salivation, and small doses of iodides a rash or oedema of the larynx or pharynx. Some examples of the drug idiosyncrasies may now be mentioned: a few grains of iodide may bring out a bullous eruption (hydroa) which is most often on the face and in the neighbourhood of the eyes, but may even appear on the tongue (Hall²). Particularly interesting are the cases of granulomatous tumours resembling

¹ Zinsser, H., *Infection and Resistance*, p. 100, New York, 1918.

² Hall, A. J., *Lancet*, 1926, ii, 952.

IDIOSYNCRASIES

multiple sarcoma and called iodide sarcoma, which in a way correspond to arsenic carcinoma, though in both these instances the tumour-like formations occur from prolonged, not single, administration of the drug. Hutchinson¹ (1900) reported several such cases, one in a man erroneously thought to have syphilis who died from exhaustion after three months' dosing with iodides. He also refers to a somewhat similar case in a man who was taking a proprietary blood mixture without his doctor's knowledge. Acute oedema of the glottis requiring tracheotomy has been known to follow 12 grains only of iodide (Hutchinson² 1894). In some persons the mere contact with iodoform brings out a bullous eruption which may be mistaken for pemphigus (Whitfield³). Bromides have produced much the same, though perhaps less extreme, skin manifestations as iodides, and have been known to produce granulomatous tumours

¹ Hutchinson, J., *Arch. Surg.*, London, 1900, xi, 158.

² *Idem. ibid.*, 1894, v., 270.

³ Whitfield, A., *Lancet*, 1921, ii, 61.

IDIOSYNCRASIES

(the mycotic type of bromoderma) on the skin, like the "iodide sarcoma," with nodules on the tongue (Weber¹).

Quinine, besides producing a rash like that of scarlet fever in some persons in small doses, has in exceptional instances been reported to cause fainting. Belladonna, toxic doses of which often bring out a similar rash, may in small doses have the same effect and cause collapse and delirium in sensitive persons. Morphine has been known to excite insomnia and convulsions, bromides mental excitement, tartrate of antimony shock and collapse (Christopherson²), and drugs of the coal tar series, such as phenazone (antipyrin), and acetanilide (antifebrin) collapse, fainting, a rash and more rarely oedema. These effects should be distinguished from their occasional haemolytic action on the blood corpuscles with the production of methaemoglobin and cyanosis. Phenolphthalein, a constituent

¹ Weber, F. P., *Brit. Journ. Derm. and Syphil.*, London, 1923, xxxv, 169.

² Christopherson, J. B., *Modern Technique in Treatment*, 1925, vol. I., p. 328.

IDIOSYNCRASIES

of many laxative preparations, may bring out urticaria. Some persons are sensitive to salicylates, and may thus manifest extra-systoles (intermittent pulse), and even mental disturbance; aspirin, in such small doses as $7\frac{1}{2}$ grains, has precipitated severe paroxysms of asthma, urticaria, and oedema, and in a person hypersensitive to aspirin it has been found that luminal and veronal had a similar effect (Storm van Leeuwen¹). As illustrating the pitfalls of drug idiosyncrasies it may be mentioned that unpleasant effects may be due to a contamination and not to the drug itself; thus a man was sensitive to one only of five different preparations of aspirin, that one being shewn to contain an impurity which was the responsible agent (Duke²). In former times contamination of potassium iodide with iodates and nitrates occurred, and may have been responsible for Huchard and Le Gendre's³ case of oedema

¹ Storm van Leeuwen, W., *Journ. Pharmacol. and Exper. Therapeut.*, 1924, xxiv, 25.

² Duke, W. W., *Allergy, Asthma, Hay Fever*, etc., p. 70, 1927, London.

³ Huchard, et Le Gendre., *Bull. et mém. Soc. méd. des hôp. de Paris*, 1885, 3 s., II. 194.

IDIOSYNCRASIES

of the glottis requiring tracheotomy. Veronal or barbitone (di-ethyl barbituric acid), also sold as malonal and hypnogen, is a somewhat dangerous hypnotic, and in exceptional cases death has followed doses of 15 grains, and in one well authenticated instance of $7\frac{1}{2}$ grains, though on the other hand recovery has taken place after 100 grains have been taken, thus suggesting a special sensitiveness in the case of the smaller dose. From inhalation of the powders of ipecacuanha, rhubarb, and lycopodium dispensers have suffered from asthma or hay fever; this has sometimes been found to develop after years of exposure—an example of acquired hypersensitiveness. Cocaine and its allies, which are so widely employed as local anaesthetics, may produce sensitiveness as shown by dermatitis in dentists, and occasionally by severe symptoms of collapse in their patients.

Arsenic when administered in small doses for the first time gives rise in rare instances to unusually well marked symptoms of irritation of mucous membranes, conjunctivitis, and abdominal pain, a

IDIOSYNCRASIES

susceptibility which appears to be life-long. The production of herpes zoster or shingles (derived from the Latin *cingulum*= a belt) by arsenic is well known, and indeed first aroused the suspicion that arsenic was responsible for the outbreak of poisoning among beer drinkers in the Midlands in 1900 (Reynolds¹) ; it is also of interest because arsenic has a selective action on the ectodermal structures—the skin and nervous system. But shingles is seen in very few of those who take arsenic, and then usually in their first course of the drug, though after an incubation period ; it might therefore be thought to be an acquired idiosyncrasy. On the other hand there is not any evidence that the herpes recurs as the result of subsequent arsenic administration.

Intravenous injections of salvarsan preparations are sometimes followed by immediate ill effects which closely resemble those of anaphylactic shock ; this may not occur until the third or subsequent

¹ Reynolds, E. S., *Med.-Chir. Trans.*, 1901, **LXXXIV**, 411.

IDIOSYNCRASIES

injection, but may follow the first dose, and as it is probable that they are due to flocculation or precipitation of the drug in the circulation it is inadvisable to invoke acquired sensitiveness or anaphylaxis as an explanation.¹

CUTANEOUS MANIFESTATIONS OF HYPERSENSITIVENESS.

Skin eruptions as evidence of idiosyncrasies or hypersensitiveness, which have been set forth in detail by Cranston Low² in the three hundred pages of his book, are frequently produced by foods and drugs. In some instances, as in angio-neurotic oedema and in its allied and less prominent form urticaria, the exciting agent may not be so obvious, and may therefore be regarded as metabolic, or produced inside the body by some defect in the chemical processes, especially those concerned with the elaboration

¹ Report of the Salvarsan Committee, No. 2, Special Report Series No. 66, Medical Research Council, 1922, p. 19.

² Low, R. Cranston, *Anaphylaxis and Sensitization with special Reference to the Skin and its Disease*, 1924.

IDIOSYNCRASIES

of proteins absorbed from the alimentary tract. As this process occurs largely in the liver, it would be interesting to know more of the results of tests for hepatic function in skin diseases such as "eczema."

"Eczema" is a well recognized manifestation in infants hypersensitive to cow's milk and other foods, and may coincide with, alternate with, or be followed by asthma later in life. Among John Thomson's¹ hundred cases of children with asthma there were more than a quarter with a history of eczema, and half of Storm van Leeuwen's² asthmatic patients had had eczema earlier in life; this observer believes that one of the main factors in the etiology of the allergic diseases, of which asthma and hay fever are the best established, is an increased permeability of the skin and mucous membranes, which allows the exciting agents ("allergens") to pass into the

¹ Thomson, J., *The Clinical Study and Treatment of Sick Children*, p. 545, 1925.

² Storm van Leeuwen, W., *Allergic Diseases* London, 1925.

IDIOSYNCRASIES

body. The position is complicated by his view that the allergens may either exert a purely sensitizing action, or first a toxic and irritant influence and so causing inflammation and then sensitization as is seen in asthma following bacterial bronchitis. As an example of how extreme acquired hypersensitiveness may become reference may be made to the case of a lecturer on chemistry who, having become sensitive to phenylhydrazin, suffered from dermatitis immediately after visiting the house of an assistant who had been handling the salt (Hallam¹).

Urticaria (Nettlerash, "Hives") is seen in the immediate reaction produced by a second injection of serum in a man rendered anaphylactic by a previous injection, and the occurrence of an urticarial wheal is utilized in the skin tests as the evidence of hypersensitiveness to the protein extract of the suspected substance. Urticaria of various durations arising spontaneously may therefore be

¹ Hallam, R., *Brit. Journ. Derm. and Syphil.*, London, 1927, xxxix, 95.

IDIOSYNCRASIES

assumed to be due to hypersensitiveness which, as shewn by its association with certain articles of food and by the frequency with which it is relieved by purgation, is often of intestinal origin. In women there appears to be a frequent association between urticaria and infection of the urinary tract with *Bacillus coli* (Whitfield¹). The papular urticaria (lichen urticatus of Bateman) of young children has been shewn by skin tests to be associated with protein sensitiveness, but what particular protein causes it has not yet been proved. In Hallam's cases it seemed to depend on home influences, for it disappeared directly the children came into hospital and returned when they went home, even if no food was taken there; dust from their homes did not excite it.

Angio-neurotic oedema (Quincke's oedema), originally well described as giant urticaria, is a somewhat bizarre condition of what Solis-Cohen² called

¹ Whitfield, A., *Lancet*, 1921, ii, 122.

² Solis-Cohen, S., *Am. Journ. Med. Sc.*, Phila., 1894, cvii, 130.

IDIOSYNCRASIES

vasomotor ataxia. It consists in the sudden appearance of transient hard swellings of the skin of the face, hands, feet, or genitals, or of the mucous membranes, especially of the larynx, which proved fatal in 36 out of W. Bulloch's¹ 170 cases in 28 families; fatal angio-neurotic oedema of the larynx has occurred in an infant of 14 months after drinking a cup of milk (Wason²). As colic may occur, the possibility of a similar change in the intestines, thus resembling Henoch's purpura (namely purpura with abdominal symptoms) is suggested. Its resemblance to urticaria, occasional association with hay fever or migraine, its tendency to recur, and hereditary character, even to the sixth generation, would appear to ally it with other allergic diseases. An irritable state of the nervous system, perhaps due to calcium deficiency, often coexists and may play a part in the production of the condition. In many

¹ Bulloch, W., *The Treasury of Human Inheritance*, Part 3, 1909.

² Wason, I. M., *Journ. Am. Med. Assoc.*, Chicago, 1926, LXXXVI, 1332.

IDIOSYNCRASIES

instances sensitization, as the result of bacterial infection, would appear to be largely responsible for its occurrence ; but this is often difficult to prove. As Lewis and Zotterman¹ have shown that acute local oedemas of the skin depend on liberation of a histamine-like substance from the epidermal cells as the result of injury of some sort, it appears highly probable that the same holds good of angio-neurotic oedema.

Pruritus, or itching without a pre-existing skin eruption, is a common and distressing affection, and may be a manifestation of idiosyncrasy to certain foods, such as shell-fish. It has been found to be associated with hypersensitiveness, as indicated by skin tests, to pork and to potatoes. In some cases of lymphadenoma pruritus is very troublesome ; this may be the first symptom, before any glandular enlargement is obvious, and so drive its victim first to a dermatologist ; possibly it is due to the production of a foreign

¹ Lewis, T., and Zotterman, Y., *Heart*, 1926, XIII, 203.

IDIOSYNCRASIES

protein in the affected lymphatic glands deep in the chest or abdomen. During the latter part of the Great War and directly afterwards laboratory investigators into mustard gas (dichlor-ethyl-sulphide) gradually became so sensitized to it that slight exposure caused violent itching followed by a scarlatiniform rash and peeling (W. E. Dixon). It is interesting to speculate whether the relief given by x-ray exposures in ordinary pruritus may be due to de-sensitization by means of liberation of some protein from the exposed epidermal cells.

In connection with dermatitis venenata, or skin eruptions due to contact with plants (vide p. 35), which Coca regards as examples of universal hypersensitiveness and so not idiosyncrasies which are by definition exceptional reactions, the suggestion was made that some of these might nevertheless be manifestations of acquired sensitiveness. Mention may therefore be made of the fur dermatitis, which has been noticed since 1922 as the result of wearing cheap rabbit skins, impregnated with dyes, round the

IDIOSYNCRASIES

neck, and ascribed to the irritation of paraphenylene-diamine or metaphe-nylene-diamine in the dye. Parsons¹ says that personal idiosyncrasy is certainly concerned in the production of symptoms in this as in other forms of dermatitis due to potential irritants, as the number of sufferers bears but a small proportion to the total of girls and women wearing these furs without bad effects. Roxburgh² who has reported on 86 cases of this fur dermatitis considers that a few patients are naturally sensitive to the irritant, but that in the great majority the sensitive-ness is acquired, as shewn by a definite incubation period before the eruption appears. Usually the eruption is confined to the parts in contact with the fur, but in some persons it is more wide-spread, and hypersensitiveness to other substances may result.

¹ Parsons, A. C., Reports on Public Health and Medical Subjects, No. 27, 1924, Ministry of Health, p. 7.

² Roxburgh, A. C., *Brit. Med. Journ.*, 1923, i, 534; *Brit. Journ. Derm. and Syphil.*, London, 1925, xxxvii, 126.

IDIOSYNCRASIES

ASTHMA

Asthma (*ἄσθμα* = panting) and the adjective asthmatic are sometimes used popularly in a loose way to describe shortness of breath of any kind, but although "asthma is dyspnoea, dyspnoea is not necessarily asthma" (T. Watson¹), and hence bronchial or spasmodic asthma is perhaps a more distinctive title for the attacks of paroxysmal dyspnoea, usually periodic, with intervals of normal respiration. It is due to spasm of the muscular walls and oedematous swelling of the mucous membrane of the bronchial tubes, and is one of the commonest examples of what were formerly called the spasmodic neuroses and more recently by John Freeman² toxic idiopathies. Hay fever is closely allied to asthma, but whereas asthma may be due to very various causes, hay fever, as the name implies, is excited by the pollens of plants. Two forms of asthma—"renal" and

¹ Watson, T., *Principles and Practice of Physic*, 1871, II, 392.

² Freeman, J., *Proc. Roy. Soc. Med.*, 1920, XVIII, 129.

IDIOSYNCRASIES

“cardiac”—may be briefly mentioned: renal asthma is asthma in cases of advanced kidney disease, and probably depends on the retention of poisons in the blood; in cardiac disease similar attacks, also usually nocturnal, are quite different from the shortness of breath on exertion in heart disease; in both “renal” and “cardiac” asthma the symptoms have been thought to be due to the sudden entry into the blood of non-volatile acid bodies (Lewis¹).

Spasmodic or bronchial asthma has long been known; the first book in English, “A Treatise on the Asthma,” was written by Sir John Floyer (1649—1734) of Lichfield in 1698, who was himself a victim and was described by his patient Samuel Johnson as having “panted on to ninety,” though in point of fact he died five years short of that age. Hyde Salter², who regarded it as essentially a nervous disease, was the first to point out that it may be excited

¹ Lewis, T., *Lectures on the Heart*, pp. lxxxi-lxxxv; and Lewis, Ryffel, Woolf, Cotton, and Barcroft, *Heart*, London, 1913-14, v, 45.

² Salter, H. Hyde, *On Asthma*, 1859, London.

IDIOSYNCRASIES

by animal emanations, especially of horses, cats, and dogs.

In 1906 Langlois¹ and Wolff-Eisner² independently suggested that the allied condition of hay fever was anaphylactic in nature, in 1910 S. J. Meltzer³ adopted this explanation for asthma; since then the view that asthma is due to hypersensitiveness to foreign proteins, whether inhaled or of bacterial origin, has occupied the field rather to the exclusion of reflex causes acting on an irritable nervous system; but this popular conception of acquired hypersensitiveness as the factor responsible for asthma has not been without its critics; Kahn⁴ considers that protein sensitiveness, though a phenomenon in many cases of asthma, is not the cause, and that the disease is always hereditary, (statistical estimates

¹ Langlois, J. P., *Presse méd.*, Paris, 1906, xiv, 583.

² Wolff-Eisner, A., *Das Heufieber*, München, 1906.

³ Meltzer, S. J., *Journ. Am. Med. Assoc.*, Chicago 1910, LV, 1021.

⁴ Kahn, M. H., *Arch. Int. Med.*, Chicago, 1927, xxxix, 621.

IDIOSYNCRASIES

on human heredity being fallacious from insufficient data) and dependent on the chromosomal constitution. Hurst's¹ definition of asthma as "the reaction of an over-excitable bronchial centre to blood borne irritants and to peripheral or psychical stimuli" has the advantage of including cases of reflex origin, prone to occur in the subjects of vagotonia, or an excitable condition of the vagus and the parasympathetic system, and as the result of emotion; for example a patient who was hypersensitive to roses and thus had attacks when brought in contact with them developed a similar attack after smelling what was really an artificial rose; W. E. Steavenson, however, in his published thesis for the M.B. degree at Cambridge (1879) wrote that he had "never been prevented by an attack of asthma from going in for or completing any examination; but when completed and the strain on my mind relieved, it has always been followed the succeeding night and day by a severe

¹ Hurst, A. F., *Lancet*, 1921, i, 1131.

IDIOSYNCRASIES

attack.”¹ In such emotional asthma the bronchial centre is in an irritable condition and it is not necessary that any foreign protein should be brought by the blood stream to irritate the centre. It has indeed been thought that an absolute vagotonia, whether inborn or acquired, explains why some persons only are hypersensitive to foreign proteins or other stimuli known to excite asthmatic attacks, and in favour of this it might be urged that asthma is so often hereditary and that, at any rate at first, the hypersensitiveness is to a group of proteins,

¹ It is interesting to note how many sufferers from asthma have published records of their experiences ; Floyer, (1698), John Arbuthnot (1733), the originator of the character of “ John Bull,” Hyde Salter (1859, Trousseau (1866), A. F. Hurst, (1921) and J. R. Charles (1925). Hay fever was also described from personal experience by John Bostock (1819) and C. H. Blackley (1873). Asthma was formerly regarded as a paroxysmal neurosis in company with migraine, which is perhaps *the* disease of distinguished men, and certainly has stimulated so many accounts from astronomers and men of the first rank in science, Sir G. Airey, Sir John Herschel, Sir D. Brewster, Sir C. Wheatstone, W. H. Wollaston, and among medical men from John Fothergill, Caleb Hillier Parry, Sir Samuel Wilks, E. Liveing, and Sir James Mackenzie.

IDIOSYNCRASIES

not to one or to the same protein as in the parent. Perhaps the safest position at present is to keep an open mind and believe that in some instances there is vagotonia alone, in others a toxic idiopathy alone, and that in others both factors are at work. It is thought that the toxic idiopathies may act by depressing adrenalin secretion which neutralizes the vagotonia.

When cutaneous tests for sensitiveness to foreign proteins contained in foods, feathers, dandruff, pollens, and bacteria were brought in, much was naturally expected from them, and I. C. Walker of Boston, Mass., obtained a positive reaction in 52 per cent. of 400 cases of asthma; but later experience has been disappointing, contradictory, and confusing; Freeman was successful in 5 per cent. of his cases, and Hurst obtained "a very small percentage of positive reactions." The failure of the skin tests is particularly noticeable in the cases of asthma due to bacterial toxins. There is as yet no ideal method for determining sensitiveness;

IDIOSYNCRASIES

the scratch method is not delicate enough, as many cases of undoubted toxic idiosyncrasies give negative results, and on the other hand the intracutaneous method gives many false reactions which may be confusing and difficult to interpret. Storm van Leeuwen's¹ asthmatic patients gave positive skin reactions to so many extracts (for example 37 per cent. of his cases reacted to more than ten extracts) that he considers skin tests useful in showing that the individual is hypersensitive, but not what particular agent or allergen is responsible. Cases of asthma have, on the basis of their reactions to cutaneous tests, been divided into the sensitive and the insensitive groups. Rackemann² found that 60 per cent. of the sensitive cases gave a family history of hypersensitiveness as against only 10 per cent. of the insensitive cases of asthma; and Cooke and Van der Veer found that the cases are inherited according to Mendelian laws.

¹ Storm van Leeuwen, W., *Allergic Diseases*, 1925.

² Rackemann, F. M., *Modern Medicine* (Osler and McCrae), 1927, iv, 78.

IDIOSYNCRASIES

Asthma may be associated with other toxic idiopathies, such as the skin eruptions urticaria and eczema, migraine, and gastro-intestinal disturbance. The analogy of mucous colic to asthma and its description as asthma of the colon has been mentioned (vide p. 59).

The numerous exciting causes of asthma may be roughly divided into (i) extrinsic, such as animal emanations, hair, flesh, vegetable pollens, odours, foods, and fungi; house and other dusts; and some chemical non-protein bodies, aspirin, for example, of which Storm van Leeuwen has studied 14 cases of violent asthma excited by $7\frac{1}{2}$ grains of this familiar drug. The animal emanations causing horse-, dog-, and cat-asthma are common; as in other cases of hypersensitiveness the condition is very specific; an instance of this may be quoted from Bastian's¹ paper on nematodes; after dissecting *Ascaris megalocephala*, a round worm found in the intestines of the horse, whether fresh or after preservation in

¹ Bastian, C., *Phil. Trans.*, 1866, cxcvi, part 2, 583.

IDIOSYNCRASIES

spirit for two years, he suffered from hay fever and later from asthma, becoming more sensitive with repeated exposures, so that at least one exposure produced an attack lasting six weeks ; he was able to dissect *Ascaris lumbricoides*, the round-worm found in man, without any reaction ; he does not say that he had ever had asthma before or was affected by horse emanations, and so it may be presumed he was not.

(ii) Intrinsic absorption from infective foci, the microbes responsible for which have come from the outer world ; various micro-organisms, streptococci and according to Eyre and Hurst especially Friedländer's pneumobacillus may be the responsible agent. Errors of metabolism, such as abnormal products of primary digestion, insufficiency of hepatic metabolism and of the endocrine glands must also be considered. In addition an irritable condition of the respiratory centre is an important factor.

The eccentricities of asthma are many and may be explicable by the occult presence and removal of the exciting

IDIOSYNCRASIES

cause ; that some persons were comfortable only in the old smoky Metropolitan Railway may have been from the absence of horse emanations there ; this is the converse of the inability of some to live in the country in the spring and summer on account of pollen. Feathers in pillows, fungi in old mattresses or ill-aired beds (Storm van Leeuwen) may account for the frequency of asthmatic seizures at night. Storm van Leeuwen¹ lays stress on the influence of products derived from fungi and yeast in the air, and explains the freedom of asthmatic patients from their affliction while in alpine and high altitudes by the absence of the atmospheric contents, a view which he has put into practice by the therapeutic use of pure air (allergen-free) sleeping chambers supplied with filtered air. It has, however, been suggested that exhaustion of the adrenals, due to fatigue during the day, may allow unrestrained activity of the vagus to occur at night (Hurst²).

¹ Storm van Leeuwen, W., *Journ. Pharmacol. and Exper. Therapeut.*, 1924, xxiv, 25.

² Hurst, A. F., *Medical Essays and Addresses*, p. 227, London, 1924.

IDIOSYNCRASIES

The scientific treatment is to remove the hypersensitive state by the process of de-sensitization, such as inoculation by minute quantities of the sensitizing agent, by very small quantities of the offending food, and in the case of bacterial infections, by autogenous vaccines, combined when feasible with removal of a septic focus. This is specific de-sensitization; but non-specific de-sensitization such as the injection of protein in the form of Witte's peptone, milk, or stock vaccines so as to produce protein-shock therapy is efficient, and it is said that autogenous vaccines given with the idea that they should exert a specific action often really produce their effect in a non-specific manner (Rackemann and Graham¹). Vaccine treatment is stated to be successful only in cases in which skin tests are positive to the vaccine; Storm van Leeuwen, who obtained positive skin tests in nearly all his cases but does not consider that this proves more than that the patient is allergic, successfully

¹ Rackemann, F. M., and Graham, L. B., *Journ. Immunol.*, 1923, VIII, 925.

IDIOSYNCRASIES

treated 50 per cent. of his cases with tuberculin.

An interesting point arises in connection with the well known effect of adrenalin injections in cutting short an asthmatic attack by stimulating the sympathetic nervous system and so abolishing the dominance of vagotonia. In some instances excitement, such as that due to public speaking, relieves persistent asthma: may this be due to an increased output of adrenalin at the time? W. E. Steavenson's experience, quoted above, that the asthma to which he was a martyr never prevented his going in for or completing an examination, though an attack always followed, might be thus explained. X-ray exposures over the spleen have been reported by American observers (Waldbott¹; Ramirez and Cole²; Gerber³) and the benefit has been explained by the view that the spleen is thus stimulated

¹ Waldbott, G. L., *Arch. Int. Med.*, Chicago, 1925, xxxvi, 743.

² Ramirez, M. A., and Cole, L. G., *Am. Journ. Roentgen.*, 1925, xiv, 322.

³ Gerber, L., *Journ. Am. Med. Assoc.*, Chicago, 1925, lxxxv, 1026.

IDIOSYNCRASIES

to an increased production of antibodies. It is conceivable that the left adrenal is also stimulated by the x-rays ; but the good results following x-ray exposures of the roots of the lung (Marum¹), and of the body generally, are against the suggestion of adrenal stimulation. That benefit follows x-ray and ultra-violet exposures is fairly well established, and has been thought to improve the metabolism of calcium, which is deficient in many cases of asthma and hay fever ; Gilbert Scott² who has reported cases much relieved by x-rays refrains from any hypothesis of the rationale, but emphasizes the administration of small doses over large areas of the body, a procedure which suggests some metabolic change or the liberation from the radiated skin of some protein body leading to de-sensitization.

HAY FEVER.

Hay fever was described as “ summer catarrh ” by John Bostock in 1819,

¹ Marum, G., *Strahlentherapie*, 1924, xviii, 849.

² Scott, G., *Brit. Med. Journ.*, 1926, i, 939.

IDIOSYNCRASIES

and given its present name by Blackley in 1873 who noticed its relation to pollen of grasses and, like Bostock, had the scientific advantage of being a victim of this form of sensitiveness. It is a seasonal form of allergic vasomotor rhinitis and consists in swelling, itching, and copious discharge from the conjunctivae and nasal mucous membrane with much sneezing. It is much like asthma, but differs in its site and in a very definite relation to pollens of various kinds. The troublesome condition tends to diminish with age, and is markedly benefited by specific treatment, namely de-sensitization by injection of small quantities of the particular pollen which in the individual brings on the attacks.

OTHER ALLERGIC DISEASES

Intermittent hydrarthrosis is rare, for about 78 cases only are on record (Miller and Lewis¹). The joints, the knees always and sometimes other joints in addition,

¹ Miller, J. L., and Lewis, P., *Journ. Am. Med. Assoc.*, Chicago, 1924, LXXXII, 1177.

IDIOSYNCRASIES

become swollen with inflammatory fluid containing leucocytes at intervals, most commonly of twelve days, with almost mathematical regularity, but are normal between the attacks. These manifestations may occur in patients with asthma, migraine, angio-neurotic oedema, or urticaria, and may indeed be associated with one of them ; this curious condition has been regarded as the arthritic form of angio-neurotic oedema, and A. E. Garrod, who holds this view,¹ has pointed out the resemblance of the arthritic manifestations accompanying the erythemas to the cutaneous rash,² so that it might be said that there was a similar condition in the two situations. Peptone injected into the skin has shewn that the reaction for hypersensitiveness is present in these patients, and a typhoid vaccine has cured the condition either by non-specific desensitization or by shock therapy (Miller and Lewis).

Migraine or megrim (hemicrania) has

¹ Garrod, A. E., *Quart. Journ. Med.*, Oxford, 1909-10, III, 20.

² *Idem.*, *Lancet*, 1911, i, 1411.

IDIOSYNCRASIES

been thought to be due to hypersensitivity; it is hereditary; asthma is said to be fairly frequent in the family history; thus Ball¹ found the association of asthma in 60 out of 261 migrainous families; eosinophilia also may occur in both. Storm van Leeuwen and Zeydner² have obtained from the blood in asthma, urticaria, epilepsy, and migraine, but not from that of normal persons, a substance which stimulates smooth muscle to contract, and so, as this is a manifestation of the anaphylactic reaction, to suggest that migraine and epilepsy are allergic diseases. It is often precipitated by errors in diet; and has been thought to be due to sensitiveness to bacterial poisons absorbed from the intestinal tract, to proteins and purines, and to carbohydrates, and has thus been found to be due to eating beans and chocolate. Among 33 cases of migraine Vaughan³ found that 12, or

¹ Ball, F. E., *Am. Journ. Med. Sc.*, Phila., 1927, CLXXIII, 781.

² Storm van Leeuwen and Zeydner, *Brit. Journ. Exper. Path.*, London, 1922, III, 282.

³ Vaughan, W. T., *Journ. Am. Med. Assoc.*, Chicago, 1927, LXXXVIII, 1383.

IDIOSYNCRASIES

36.4 per cent., were due to hypersensitiveness to some form of food. Another argument, for what it is worth, in favour of its dependence on hypersensitiveness to foreign proteins is that it has been cured by peptone ($7\frac{1}{2}$ grains) given by the mouth before food (Vallery-Radot¹; Lubbers), or injected hypodermically (Miller and Raulston²). It has been argued that some cases of migraine are reflex angiospasm due to atonic distention of the gall bladder (Vallery-Radot and Blamoutier³; Chiray and Lomon⁴), and that the relief obtained by non-surgical drainage of the gall bladder by Lyon's method supports this view. In the present state of our knowledge it would be wise to be content with the suggestion that some cases only of migraine, as of epilepsy, may be due to hypersensitiveness to proteins.

¹ Vallery-Radot, P., *Médecine*, Paris, 1923, iv, 371.

² Miller, J. L., and Raulston, B. O., *Journ. Am. Med. Assoc.*, Chicago, 1923, LXXX, 1894.

³ Vallery-Radot, P., et Blamoutier, P., *Bull. et mém. Soc. méd. des hôp. de Paris*, 1927, 3e. sér., LI, 925.

⁴ Chiray, M., et Lomon, A., *Ibid.*, p. 932.

IDIOSYNCRASIES

Crookshank¹ has insisted on its psychological origin, but, even at the risk of going to a materialistic extreme, it is perhaps well to draw attention to the possibility that there is a bio-chemical basis for some cases of migraine. There is similarity between migraine and epilepsy the first being the sensory equivalent of the convulsive motor manifestations of the other ; Hurst² argues that asthma epilepsy, and migraine are much alike in all depending on a constitutional and frequently hereditary irritable focus in the brain, but that the constitutional basis in each of them is specific and that they are not, as has been sometimes stated, interchangeable in generations and members of the same family or in the same individual. Among 261 families with migraine in some member there were 10 examples of epilepsy or 4 per cent. only (Ball).

¹ Crookshank, F. G., *Migraine and other Common Neuroses* : " Psyche " Miniature Medical Series, No. 1., 1926, London, Kegan Paul, Trench, Trubner and Co.,

² Hurst, A. F., *Brit. Med. Journ.*, 1927, i, 868.

IDIOSYNCRASIES

Epilepsy is a reaction produced by various causes, and therefore not a specific disease ; there are in fact many epilepsies; some cases of course depend on an organic lesion, such as a tumour, sclerosis, or injury ; others are due to poisons, for example absinthe and alcohol ; abnormal products, such as may result from disturbed function of the liver (McClure and Huntsinger¹) or of the parathyroids, have been assumed to excite epileptic attacks in a manner analogous to uraemic convulsions. Alkalosis due to parathyroid insufficiency has been regarded as a cause (Bigwood²), and accordingly a diet that produces a well-marked ketonuria has been employed with benefit, at any rate in children (Talbot, Metcalf, and Moriarty³) ; in this connection it may be noted that luminal rapidly diminishes the alkalinity of the blood,

¹ McClure, C. W., and Huntsinger, M. E., *Boston Med. and Surgical Journ.*, 1927, cxcvi, 270.

² Bigwood, E. J., *Ann. de méd.*, Paris, 1924, xv, 119.

³ Talbot, Metcalfe, and Moriarty, *Boston Med. and Surg. Journ.*, 1927, cxcvi, 89.

IDIOSYNCRASIES

whereas bromides do not do so but only depress nervous activity. But there is one group of epileptics which Craig¹ has isolated as due to hypersensitiveness, as shewn by skin tests, to various proteins ; these patients do not respond to, in fact may be made worse by, bromides ; but if the exciting food is avoided do not need any other treatment ; in these selected patients the evidence of sensitization, as shewn by skin tests, was found by Mackenzie Wallis to vary, being well marked before and absent immediately after a seizure. It may be mentioned in this connection that violent toxic psychoses have been excited in persons sensitive to mushrooms, shell-fish, and pork (Craig and Beaton²).

¹ Wallis, R. L. M., and Nicol, W. D., and Craig, M., *Lancet*, 1923, i, 741.

² Craig, M., Beaton, T., *Psychological Medicine*, p. 187, 1926.

DISEASES POSSIBLY ALLERGIC OR DUE TO HYPERSENSITIVENESS.

This subject is at once attractive and dangerous from the temptation to speculate beyond the bounds of the available data. Some joint affections may be briefly mentioned first; gout is a disease of purine metabolism, and it may appear premature to suggest that hypersensitiveness has anything to do with its manifestations. But it is notoriously hereditary, the subjects of gout are specially prone to food idiosyncrasies, and gout is not uncommon in persons who also suffer from migraine, eczema, or asthma. There is some evidence that the acute attacks of gouty (chemical) arthritis occur in association with septic foci elsewhere, so that it might be suggested that the joints have thus become sensitized, and that the acute attack is partly due to this and partly to the disordered purine metabolism.

IDIOSYNCRASIES

Lewis and Grant's¹ observation that, in an asthmatic patient in whom fish produced a rash, the responsible substance in the fish appeared to be chiefly associated with nucleic acid, would appear to have a definite bearing on the hypothesis that gout may be anaphylactic in nature.

In the incidence of both gout and chronic rheumatoid arthritis, which may coincide in the same individual, diathesis and predisposition play a considerable part ; in the case of rheumatoid arthritis there are numbers of people with sufficient focal sepsis, especially dental and tonsillar, who do not develop that disease. In such cases the resistance may be broken down by illness, such as influenza, and the person becomes sensitive so the morbid changes start and may progress rapidly. When the joints and fibrous tissues thus become sensitized a remnant of the focal sepsis left will suffice to keep the process active. The mechanism whereby focal infection, such as dental or tonsillar, is able to cause

¹ Lewis, T., and Grant, R. T., *Heart*, London, 1926, XIII, 219.

IDIOSYNCRASIES

the manifestations and structural changes of rheumatoid arthritis and fibrositis is commonly regarded as "diminished resistance," which after all is a synonym of acquired hypersensitiveness. In their recent book Thomson and Gordon¹ cautiously suggested that idiosyncrasy plays a part in both gout and rheumatoid arthritis, but have not found that skin tests for protein sensitiveness are of outstanding help in gout.

The exanthematous fevers, small-pox, vaccinia, measles, and scarlet fever, have been thought to be due to hypersensitiveness to the products of the responsible virus; Pirquet and Schick, as the outcome of their work on serum sickness, considered that during the incubation periods of such fevers antibodies are produced, and that when they interact with the antigen (or provocative body = the virus) there is produced a poison, called by Richet apotoxin, which causes the symptoms. Schick did not include

¹ Thomson, F. G., and Gordon, R. G., *Chronic Rheumatoid Diseases*, pp. 8, 114; 1926, Oxford Medical Publications.

IDIOSYNCRASIES

scarlet fever as he considered the incubation period too variable, and applied this explanation only to its complications. Bristol¹ has pointed out the resemblance between the clinical manifestations of serum sickness (vide p. 32), drug idiosyncrasies (vide p. 70), and scarlet fever and from a number of skin tests draws the conclusion that scarlet fever is a compound condition, first of a local streptococcic infection, usually of the throat, which produces a secondary streptococcic protein intoxication in those who are hypersensitive to it. His conclusions that scarlet fever is due to infection with a special type of *Streptococcus haemolyticus*, and that persons susceptible or insusceptible to it can be detected by skin tests, and those susceptible to it protected against it, have been established by the work of George and Gladys Dick.² These observers devised a test in which intradermic injections

¹ Bristol, L. D., *Am. Journ. Med. Sc.*, Phila., 1923, CLXVI, 853.

² Dick, G. F., and G. H., *Journ. Am. Med. Assoc.*, Chicago, 1923, LXXXI, 1166 ; 1924, LXXXII, 265.

IDIOSYNCRASIES

of a filtrate of a culture of the streptococcus shewed whether an individual was susceptible or insusceptible. Those shewn to be hypersensitive can be injected subcutaneously with the filtrate of a culture of the causative streptococcus in order to render them insusceptible.

INDEX

- Acetanilide, 79
 Adrenalin, in asthma, 102
 Adrenals and asthma, 100
 Allergens, 84
 Allergy, 13-14
 Amblyopia, tobacco, 40
 Anaemia, aplastic, 56
 Anaphylactoid reactions, 47, 50, 72
 Anaphylaxis, 14-15, 35, 45, 47, 73, 75
 Anergia, 14
 Angio-neurotic Oedema, 60, 66, 86-88
 Angiospasm, and Migraine 107
 Antipathies, 23-27
 Antipyrin, 79
 Apotoxin, 113
 Appendicitis, 69
 Arachnidism, 37
 Arsenic 76, 81-82
 Arthralgia, 32
 Arthritis, seric, 34; chronic rheumatoid, 112
 Aspirin, 76, 80, 98
 Asthma, 58, 66, 74, 80, 84, 91-102; bacterial, 47, 85, 96, 99; cardiac, 92; cat, 61, 98; definition of, 94; dog, 61, 98; emotional, 95; horse, 61, 98; reflex, 93; renal, 92; sufferers from, 95; treatment of, 100.
 Ataxia, vasomotor, 87
 Atopens, 43
 Atopia, 43
 Barbitol, 81
 Beans, 61, 106
 Belladonna, 70, 76, 79
 Bromides, 71, 78
 Brown, T., 26
 Cabbage, 68
 Calomel, 11, 71, 77
 Carrots, 68
 Cat—asthma, 98
 Cats, horror of, 23
 Cheese, 24
 Chocolate, 68, 106
 Cocaine, 76, 81
 Colic, mucous, 59, 66
 Colitis, mucous, 59
 Constitution, 17-19
 Dandruff, 46, 96
 Deafness, tobacco, 40
 Death, anaphylactic, 33, 35, 45
 Dermatitis, fur, 89-90; solar, 55; venenata, 35
 De-sensitization, 46, 63, 89; non-specific, 101, 104, 105
 Diathesis, 15-17
 Diseases, possibly allergic, 111-115
 Dick test, 114-115
 Diet, 65; and epilepsy, 109-110; and migraine, 106

INDEX

- Drug idiosyncrasies, 70-83
- Dust, house, 61, 74
- Dyspepsia, 68
- Eccentricity, 22
- Eczema, 61, 66, 68, 84
- Eggs, 63, 65
- Emanations, animal, 61, 93, 98
- Emotion and asthma, 95
- Enterospasm, 59
- Epilepsy, 42, 58, 107, 108, 109-110
- Feathers, 96, 100
- Fell, John, 26
- Fevers and allergy, 113
- Fibrositis, 113
- Figs, 67
- Fish, 24, 64
- Food, idiosyncrasies, 62-69
- Fungi, and asthma, 100
- Fur dermatitis, 89-90
- Gall-bladder and migraine 107
- Gas, Mustard, 89
- "H-substance", 51
- Haematoporphyria, 52
- Hay Fever, 61, 91, 95, 103-104
- Henoch's purpura, 33, 61, 69, 87
- Heredity, 42, 95
- Herpes, 82
- Histamine-like substance, 51, 59, 88
- Hives, 85
- Honey, 11, 67
- Horse-asthma, 98
- Hydrarthrosis, intermittent, 104-105
- Hydroa, 70, 77; Vaccini-forme, 52-54, 73
- Hydrophobias, natural, 25
- Hypersensitiveness, 30-49, abnormal, 41; acquired, 44-48, 57, 81, 85, 89, 113; atopic, 43; bacterial, 47; hereditary, 43; inborn, 42-44; manifestations of, 58; normal, 31-41
- Hyposensitiveness, 20, 30, 36
- Gooseberries, 67
- Gout, 67, 111-112
- Idiopathies, toxic, 42, 91, 98
- Idiosyncrasies, acquired, 81; drug, 70-83; food, 62-69; mental, 22-27; physical, 21; physiological, 28 *et seq.*; psychological, 22-27
- Idiosyncrasy, Definition, 11; Derivation, 7; See also Hypersensitiveness
- Immunity, 48
- Infection, and hypersensitiveness, 47
- Iodides, 70, 76-78, 80
- Iodoform, 78

INDEX

- Ipecacuanha, 81
 Itching, 88
 Ivy, poison, 35

 Lichen urticatus, 86
 Light, sensitiveness of
 skin to, 53
 Lilies, 35
 Luminal, 80, 109
 Lymphadenoma, pruritus
 in, 88
 Lymphatism, 33, and
 asthma, 43

 Malformations, 12 ; Chem-
 ical, 18
 Metabolism, errors of, 83,
 99 ; inborn errors of,
 18
 Migraine, 42, 105-108 ;
 Sufferers from, 95
 Milk, 66, 84
 Morphine, 40, 71, 79
 Mushrooms, 110
 Mustard gas, 89

 Neurosis, spasmodic, 91,
 95
 Nicotine, 40

 Oatmeal, 68
 Ochronosis, 73
 Oedema, 32, 58, 80 ;
 Angio-neurotic, 60, 66
 86-88 ; Glottidis, 78,
 80-81, 87
 Operations on hypersen-
 sitives, 68
 Oysters, 64

 Pain, sensitiveness to, 29
 Peptone, de-sensitization
 by, 101, 107
 Phenolphthalein, 79
 Phenylhydrazin, 85
 Physical factors, and sen-
 sitiveness, 50
 Poison, nature of, 37
 Pollens, 74, 96, 100, 104
 Pork, 88, 110
 Porphyrinuria, 53, 72
 Potatoes, 88
Primula obconica, 35
 Proteins, 24, 31, 45, 49,
 50, 71, 73, 75, 93, 107
 Protein shock therapy,
 101, 105
 Prurigo, Summer, 52, 55
 Pruritus, 59, 67, 88
 Purpura 33, 61, 87

 Quinine, 71, 79

 Radio-dermatitis, 55
 Radium, 55
 Rashes, 32-35, 58, 83-90 ;
 Serum, 32, 34
 Reagents, atopic, 43
 Rhinitis, allergic, 66, 104
 Rice, 67

 Salicylates, 76, 80
 Salvarsan, 82
 Sarcoma, iodide, 78
 Sensimeter, 30
 Serum-disease, 32
 Serums, 31, 44, 46
 Shell-fish, 88, 110
 Shock, anaphylactic, 38,
 45

INDEX

- Shock-therapy, 101, 105
Skin eruptions, 32-35,
58, 83-90 ; Light, sen-
sitiveness to, 53 ; Per-
meability of, 84 ; Tests,
48, 96
Smoking, 38-41
Spider-poisoning, 37
Statuscatarrhalis, 44 ;
lymphaticus, 33, 43
Strawberries, 67
Structure, congenital idio-
syncrasies of, 12
Sulphonal, 73

Tarantula, 38
Temperament, 19-20

Tests, skin, 48, 96
Tics, 22
Tobacco, 38-41
Tolerance, 11, 20, 76
Tulips, 35

Urticaria, 51, 60, 80, 85-86
Ultra-violet rays, 51, 103

Vaccines, in asthma, 101
Vagotonia, 46, 95
Veal, 67
Veronal, 81

X-rays, 55 ; and idio-
syncrasy, 56 ; in treat-
ment of asthma, 102

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